

(19) World Intellectual Property Organization
International Bureau

[bar code]

(43) International Publication Date:
November 11, 2004 (11.11.2004)

PCT

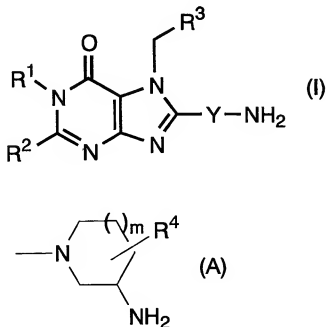
(10) International Publication Number
WO 2004/ 096806 A1

- (51) International Patent Classification⁷: C07D 473/30, 473/18, 473/06, 473/04, 473/22, A61K 31/52, 31/5377, A61P 43/00, 29/00, 19/02, 37/06, 1/00, 3/04, 31/18, 35/04, 13/08, 19/10
- (21) International Application No.: PCT/JP2004/006104
- (22) International Filing Date: April 27, 2004 (27.04.2004)
- (25) Filing Language: Japanese
- (26) Publication Language: Japanese
- (30) Priority Data:
Patent Application No. 2003-125715
April 30, 2003 (30.04.2003) JP
Patent Application No. 2003-352423
October 10, 2003 (10.10.2003) JP
- (71) Applicant(*All except US*): SUMITOMO
PHARMACEUTICAL CO., LTD. [JP/JP]; 2-2-8 Dosho-machi,
Chuo-ku, Osaka-shi, Osaka 5418510
- (72) Inventors; and
(75) Inventors/Applicants (*for US only*): NAKAHIRA, Hiroyuki
- (74) Agent: ISOBE, Yutaka; c/o Sumitomo Pharmaceutical
Co. Ltd., Intellectual Property Division, 3-1-98
Kasugadenaka, Konohana-ku, Osaka-shi, Osaka
5540022 (JP)
- (81) Designated countries: (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
- (84) Designated states (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ,

[see continuation sheet]

(54) [original English:] Title: FUSED IMIDAZOLE DERIVATIVE

(54) Title: FUSED IMIDAZOLE DERIVATIVE



(57) [original English:] **Abstract:** A compound represented by the following formula (I), a prodrug thereof, or a pharmaceutically acceptable salt of either. The compound has high DPP-IV inhibitory activity and has been improved in safety, toxicity, etc. (I) [In the formula, R¹ represents hydrogen, optionally substituted alkyl, etc.; R² represents hydrogen, optionally substituted alkyl, optionally substituted aryl, etc.; R³ represents hydrogen optionally substituted aryl, etc.; and -Y-NH₂ represents, e.g., a group represented by the formula (A) (wherein m is 0, 1, or 2; and R⁴ is absent or one or two R⁴'s are present, the R⁴'s each independently representing optionally substituted alkyl, etc.).]

[see continuation sheet]

TZ, UG, ZM, ZW), Eurasia (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europe (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

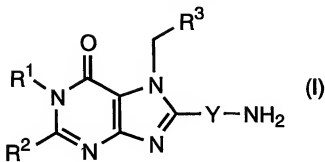
Published

— With International Search Report.

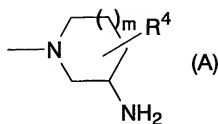
For two-letter codes and other abbreviations, refer to the "Guidance Notes on codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(57) Abstract:

To provide compounds represented by the following Formula (I), prodrugs thereof, or pharmaceutically acceptable salts of either, in the form of safer, less toxic compounds having high DPP-IV-inhibiting activity.



[Where R¹ is a hydrogen atom, an optionally substituted alkyl group, or the like. R² is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted aryl group, or the like. R³ is a hydrogen atom, and optionally substituted aryl group, or the like. -Y-NH₂ represents groups represented by Formula (A)]



(where m is 0, 1, or 2, and R⁴ may be absent or present in a number of 1 or 2, each independently an optionally substituted alkyl group, etc.).]

SPECIFICATION**FUSED IMIDAZOLE DERIVATIVE**TECHNICAL FIELD

The present invention relates to novel fused imidazoles that are useful as pharmaceuticals, and in particular to novel fused imidazoles that are effective as dipeptidyl peptidase-IV (DPP-IV) inhibitors, as well as to therapeutic agents for diabetes in which an active ingredient is a novel fused imidazole that is effective as a dipeptidyl peptidase-IV (DPP-IV) inhibitor.

PRIOR ART

DPP-IV, a serine protease occurring widely throughout the body, is a type of dipeptidyl aminopeptidase that cleaves N-terminal dipeptides through hydrolysis, and is also known as prolyl endopeptidase because of its particularly potent action on peptides in which the second amino acid from the N terminal is proline. Various biologically derived peptides involved in the endocrine system, neuroendocrine system, and immune functions are known substrates of DPP-IV. A number of physiologically active peptides serve as substrates of DPP-IV, such as the pancreatic polypeptide family, including pancreatic polypeptides (PP) and neuropeptide Y (NPY), and the glucagon/VIP family, including vasoactive intestinal polypeptides (VIP), glucagon-like peptide-1 (GLP-1), glucose-dependent insulintropic polypeptides (GIP) and growth hormone-releasing factors (GRF), as well as the chemokine family, and they are known to undergo the effects of activation/inactivation, metabolic stimulation, and the like (J. Langner and S. Ansorge, Ed., "Cellular Peptidases in Immune Functions and Disease: 2," Advances in Experimental Medicine and Biology, Vol. 477).

DPP-IV cleaves two amino acids (His-Ala) from the N-terminal of GLP-1. Although the cleaved peptide binds weakly to GLP-1 receptors, it is known to act as an antagonist, with no action in activating the receptors (L.B. Knudsen, et al, European Journal of Pharmacology, Vol. 318, pp. 429-435, 1996). GLP-1 is known to be metabolized very

rapidly in blood by DPP-IV, and the inhibition of DPP-IV is expected to result in higher concentrations of active GLP-1 in blood (T.J. Kieffer, et al, Endocrinology, Vol. 136, pp. 3585-3596, 1995). GLP-1 is a peptide that is intestinally secreted as a result of sugar intake, and is a major factor involved in glucose-induced insulin secretion in the pancreas. GLP-1 is also known to augment insulin synthesis in pancreatic β -cells as well as β -cell growth. It is also known that GLP-1 receptors are expressed in the gastrointestinal tract, liver, muscles, adipose tissues, and the like. In these tissues, GLP-1 is also known to have action on gastrointestinal activity, gastric acid secretion, glycogen synthesis and degradation, insulin-dependent glucose uptake, and the like. Increases in blood GLP-1 concentration as a result of DPP-IV inhibition can therefore be expected to stimulate blood glucose-dependent insulin secretion, improve pancreatic function, improve postprandial hyperglycemia, improve abnormal glucose tolerance, improve insulin resistance, and so forth, which should be effective in the treatment of type II diabetes (non-insulin-dependent diabetes) (R.A. Pederson, et al, Diabetes, Vol. 47, pp. 1253-1258, 1998).

Various DPP-IV inhibitors have been reported, such as the xanthine derivatives with piperazine rings, etc., reported to be effective DPP-IV inhibitors in WO 02/02560. Xanthine derivatives with piperidine rings, etc., have been reported as being effective DPP-IV inhibitors in WO 02/068420 and WO 03/004496. Xanthine derivatives with 2-aminocyclohexylamino groups have been reported as effective DP-IV inhibitors in WO 03/024965. Xanthine derivatives have been reported as effective phosphodiesterase V inhibitors in WO 02/024698.

SUMMARY OF THE INVENTION

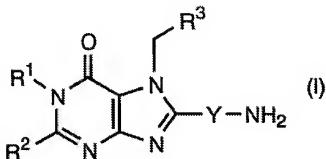
An object of the present invention is to provide novel compounds having better DPP-IV-inhibiting activity.

As a result of extensive research to address the above object, the inventors perfected the present invention upon discovering that the following compounds, prodrugs thereof,

or pharmaceutically acceptable salts thereof (also collectively referred to below as compounds of the invention, as needed) had better DPP-IV-inhibiting action.

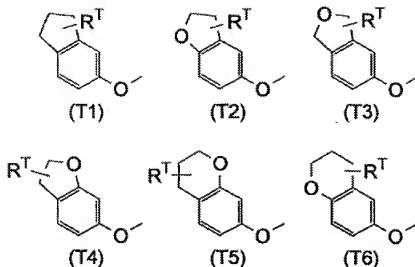
That is, the present invention relates to:

[1] Compounds represented by Formula (I), prodrugs thereof, or pharmaceutically acceptable salts thereof.



[Where R^1 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

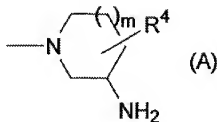
R^2 is a hydrogen atom, a halogen atom, a cyano group, a formyl group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkyloxy group, an optionally substituted alkenyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted alkoxy carbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aryloxy carbonyl group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted arylthio group, an optionally substituted arylsulfinyl group, an optionally substituted arylsulfonyl group, an optionally substituted alkylthio group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, or an optionally substituted nitrogen-bearing saturated heterocyclic group, or a group represented by (T1) through (T6) below:



(where R^T may be absent or present in a number of 1 or more, each independently being a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, a carboxy group, an optionally substituted alkoxycarbonyl group, a saturated heterocyclic group, an oxycarbonyl group, or an optionally substituted carbamoyl group, or two R^T groups together may represent methylene, ethylene, trimethylene, tetramethylene, or butenylene, and may be bonded to 1 or 2 ring-forming carbon atoms to form a new ring);

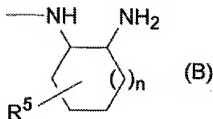
R³ is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted vinyl group, an optionally substituted nitrogen-bearing saturated heterocyclic group, or an optionally substituted heteroaryl group; and

-Y-NH₂ is a group represented by the following Formula (A) or a group represented by the following Formula (B).



(where m is 0, 1 or 2, and R⁴ may be absent or present in a number of 1 or 2, each independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl

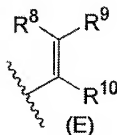
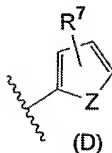
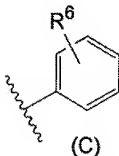
group, an optionally substituted alkoxy carbonyl group, or an optionally substituted carbamoyl group, or two R^4 groups together may represent methylene or ethylene, and may be bonded to two ring-forming carbon atoms to form a new ring),



(where n is 0, 1 or 2, and R^5 may be absent or present in a number of 1 or 2, each independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxy carbonyl group, or an optionally substituted carbamoyl group, or two R^5 groups together may represent methylene or ethylene, and may be bonded to two ring-forming carbon atoms to form a new ring).]

[2] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [1], wherein $-Y-NH_2$ is a group represented by Formula (A), and m is 1 or 2, or $-Y-NH_2$ is a group represented by Formula (B), and n is 1 or 2.

[3] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [1] or [2], wherein R^3 is any of the groups of Formulas (C), (D), or (E) below.



(where Z is an oxygen atom, $-S(O)p-$, or $-N(R^{11})-$),

R⁶ may be absent or present in a number of 1 or 2, each independently a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, a haloalkoxy group, an optionally substituted amino group, an optionally substituted carbamoyl group, an alkoxycarbonyl group, an optionally substituted alkylcarbonyl group, a cycloalkylcarbonyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group, or two R⁶ groups together may represent a C₁ to C₃ alkylenedioxy group,

R⁷ may be absent or present in a number of 1 or 2, each independently a halogen atom, a cyano group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, or a haloalkoxy group,

R⁸ is methyl, ethyl, a chlorine atom, or a bromine atom,

R⁹ is a hydrogen atom, methyl, ethyl, a chlorine atom, or a bromine atom,

R¹⁰ is a hydrogen atom, methyl, or ethyl,

p is 0, 1 or 2, and

R¹¹ is a hydrogen atom or an alkyl group.)

[4] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [3], wherein R³ is Formula (C) or Formula (E).

[5] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [4], wherein R³ is Formula (C), and R⁶ may be absent or present in a number of 1 or 2, each independently a halogen atom, a cyano group, an alkylthio group, an alkylsulfonyl group, a C₁ to C₃ alkylenedioxy group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, a haloalkoxy group, an alkoxycarbonyl group, an alkylcarbonyl group, a haloalkylcarbonyl group, or a cycloalkylcarbonyl group.

[6] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [4], wherein R³ is Formula (C), and R⁶ is one halogen atom.

[7] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [4], wherein R³ is 2-chlorophenyl, 2-chloro-5-fluorophenyl, 2-methyl-5-fluorophenyl, 2-methoxy-5-fluorophenyl, or 2-cyano-5-fluorophenyl.

[8] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [7], wherein R^1 is a hydrogen atom, a C_1 to C_3 optionally substituted alkyl group, or an optionally substituted aryl group, and the substituents for the optionally substituted alkyl groups are selected from a fluorine atom, optionally substituted aryl groups, a carboxyl group, optionally substituted alkoxycarbonyl groups, optionally substituted aryl groups, and optionally substituted aryloxy groups.

[9] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [7], wherein R^1 is a group represented by the formula $-Ra-Rb-Rc$. Where,

Ra is an alkylene chain,

Rb is a single bond or a carbonyl group, and

Rc is an optionally substituted alkyl group, an optionally substituted alkoxy group, an optionally substituted aryl group, or an optionally substituted aryloxy group.

[10] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [7], wherein R^1 is a hydrogen atom, methyl, or ethyl.

[11] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [7], wherein R^1 is methyl.

[12] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [11], wherein R^2 is a hydrogen atom, a cyano group, an optionally substituted alkyl, a carboxy group, an optionally substituted alkoxy group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, and optionally substituted alkoxycarbonyl group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aryl group, or an optionally substituted alkylcarbonyl group.

[13] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [11], wherein R^2 is a cyano group, an optionally substituted alkoxycarbonyl group, or an optionally substituted aryloxy group.

[14] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [13], wherein R^2 is a substituted aryloxy group.

[15] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [11], wherein R^2 is a substituted heteroaryloxy group.

[16] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [11], wherein R^2 is a group represented by (T1) through (T6).

[17] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [11], wherein R^2 is a group represented by the formula -O-Tx-O-Ty (where O is an oxygen atom, Tx is a phenylene group, a pyridinediyl group, a pyrimidinediyl group, or a thiophenediyl group, and Ty is an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, or an optionally substituted saturated heterocyclic group).

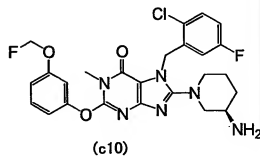
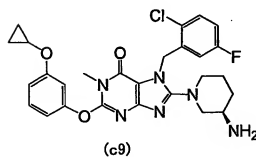
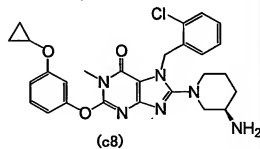
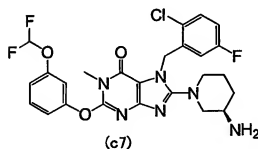
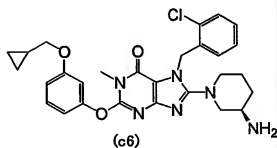
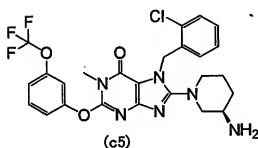
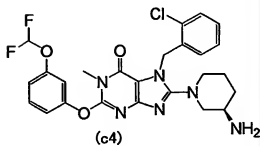
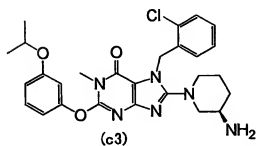
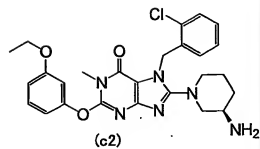
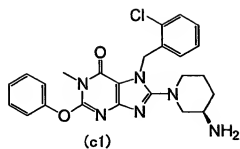
[18] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [17], wherein Tx is a phenylene group.

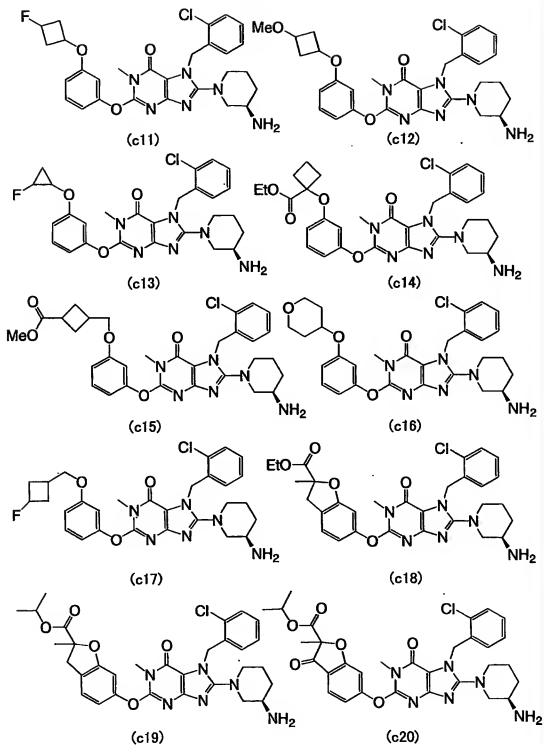
[19] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [18], wherein Tx is m-phenylene.

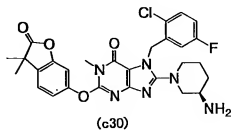
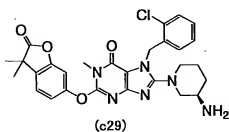
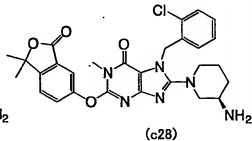
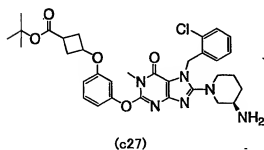
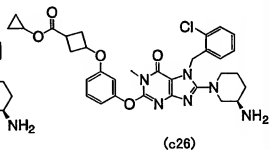
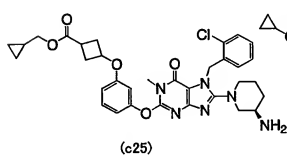
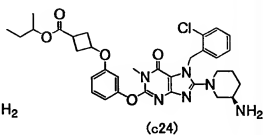
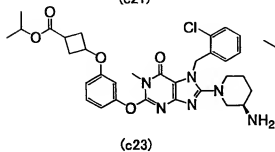
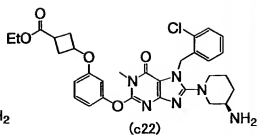
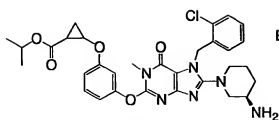
[20] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [19], wherein Ty is a substituted alkyl group, a substituted cycloalkyl group, or an optionally substituted cycloalkylalkyl group.

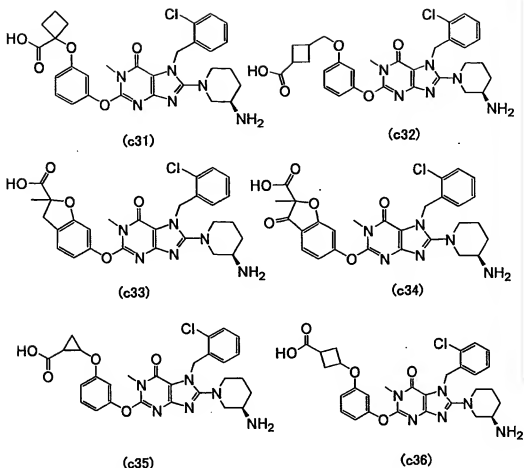
[21] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to [20], wherein the substituents for groups represented by Ty are halogen atoms, carboxy groups, or alkoxycarbonyl groups.

[22] Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof









according to [1], wherein compounds represented by Formula (I) are the following Formulas (c1) through (c36):

[23] Pharmaceuticals comprising as an active ingredient a compound, prodrug thereof, or pharmaceutically acceptable salt thereof according to any of [1] through [22].

[24] Dipeptidyl peptidase-IV inhibitors comprising as an active ingredient a compound, prodrug thereof, or pharmaceutically acceptable salt thereof according to any of [1] through [22].

[25] Therapeutic agents for diabetes comprising as an active ingredient a compound, prodrug thereof, or pharmaceutically acceptable salt thereof according to any of [1] through [22].

[26] Uses of compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [22] to produce dipeptidyl peptidase-IV inhibitors.

[27] Uses of compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof

according to any of [1] through [22] to produce therapeutic agents for diabetes. [28] Methods for treating diabetes, comprising the administration of effective amounts of compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of [1] through [22] to patients requiring treatment.

The compounds of the present invention have better DPP-IV-inhibiting activity and are useful as agents for treatment diabetes. The compounds of [16] and [17] in particular have better oral absorption.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is described in further detail below.

In the present Specification, the number of substituents for each group defined as “optionally substituted” or “substituted” is one or more, and is not particularly limited so long as substitution is possible.

When there is a plurality of R^T , or a plurality of substituents, the plurality is 2 or more, and is preferably 2, 3, 4, or 5. Even more preferable are 2 or 3.

Unless otherwise specified, the term “lower” for the alkyl moieties of “lower alkyl groups,” “lower alkoxy groups,” and “lower alkylcarbonyls” means alkyl groups, alkoxy groups, or the like having 1 to 6 carbons.

Examples of alkyl groups for the “optionally substituted alkyl groups” of R^1 and R^2 include linear or branched lower alkyl groups, etc. Specific examples include linear or branched C_1 to C_6 alkyl groups, etc. More specific examples include methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl, etc.

Examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 include (1) halogen atoms, (2) optionally substituted nitrogen-bearing heteroaryl groups, (3) optionally substituted aroyl groups, (4) optionally substituted arylaminocarbonyl groups, (5) optionally substituted nitrogen-bearing heteroarylcarbonyl groups, (6) optionally substituted nitrogen-bearing heteroarylaminocarbonyl groups, (7) carboxy groups, (8) optionally substituted alkoxy carbonyl groups, (9) optionally substituted

carbamoyl groups, (10) optionally substituted cycloalkyl groups, (11) optionally substituted aryl groups, (12) optionally substituted aryloxy groups, (13) optionally substituted arylsulfonyl groups, (14) alkylsulfonyl groups, (15) optionally substituted aralkylsulfonyl groups, (16) hydroxyl groups, or (17) optionally substituted alkoxy groups.

(1) Examples of halogen atoms include fluorine, chlorine, bromine, and iodine atoms.

(2) Examples of nitrogen-bearing heteroaryls for "optionally substituted nitrogen-bearing heteroaryl groups" include groups of 5- to 10-member rings with 1 to 2 nitrogen atoms. Specific examples include pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, triazolyl, triazinyl, tetrazolyl, indolyl, and imidazo[1,2-a]pyridyl.

Examples of substituents for "optionally substituted nitrogen-bearing heteroaryl groups" include:

(a) hydroxyl groups,

(b) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),

(c) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₆ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),

(d) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched C₁ to C₄ alkyl groups, more specifically, methyl,

ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(e) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(f) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(g) cyano groups,

(h) carboxy groups,

(i) alkoxycarbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, or butoxy)-substituted carbonyl groups; specifically, methoxycarbonyl or ethoxycarbonyl),

(j) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl),

(k) aryl groups (such as phenyl, 1-naphthyl, or 2-naphthyl), or

(l) amino groups.

(3) Examples of aryl groups for "optionally substituted aryl groups" include C₁₁ or

lower arylcarbonyl groups, and more specifically benzoyl or naphthoyl.

Examples of substituents for "optionally substituted aroyl groups" include:

- (a) hydroxyl groups,
- (b) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (c) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₆ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),
- (d) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),
- (e) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),
- (f) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more

specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(g) cyano groups,

(h) carboxy groups,

(i) alkoxy-carbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, or butoxy)-substituted carbonyl groups; specifically, methoxy-carbonyl or ethoxy-carbonyl),

(j) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl),

(k) alkylsulfonfyl groups (such as methylsulfonfyl),

(l) methylenedioxy,

(m) ethylenedioxy,

(n) nitrogen-bearing saturated heterocyclic groups (such as pyrrolidinyl, piperidinyl, or morpholinyl),

(o) cycloalkyloxy group- (such as lower cycloalkyloxy group, specifically C₃ to C₁₀ cycloalkyloxy group, more specifically cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, adamantyloxy, or norbornyloxy)-substituted alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, cyclopropyloxymethoxy, cyclobutyloxymethoxy, or cyclopropyloxyethoxy),

(p) cycloalkyloxy groups (such as lower cycloalkyloxy groups, specifically C₃ to C₁₀ cycloalkyloxy groups, more specifically cyclopropyloxy, cyclobutyloxy, cyclopentyloxy,

cyclohexyloxy, cycloheptyloxy, adamantyloxy, or norbornyloxy), or

(q) amino groups.

(4) Examples of aryl groups for “optionally substituted arylaminocarbonyl groups” include phenyl, 1-naphthyl, or 2-naphthyl.

Examples of substituents for “optionally substituted arylaminocarbonyl groups” include those given as examples of substituents for “optionally substituted aroyl groups” in (3).

(5) Examples of nitrogen-bearing heteroaryls for “optionally substituted nitrogen-bearing heteroaryl groups” include those given as examples of nitrogen-bearing heteroaryls in (2) “optionally substituted nitrogen-bearing heteroaryls.”

Examples of substituents for “optionally substituted nitrogen-bearing heteroarylcarbonyl groups” include those given as examples of substituents for “optionally substituted nitrogen-bearing heteroaryls” in (2).

(6) Examples of nitrogen-bearing heteroaryls for “optionally substituted nitrogen-bearing heteroarylaminocarbonyl groups” include those given as examples of nitrogen-bearing heteroaryls in (2) “optionally substituted nitrogen-bearing heteroaryls.”

Examples of substituents for “optionally substituted nitrogen-bearing heteroarylaminocarbonyl groups” include those given as examples of substituents for “optionally substituted nitrogen-bearing heteroaryls” in (2).

(8) Examples of alkoxycarbonyl groups for “optionally substituted alkoxycarbonyl groups” include C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, 2-propoxy, butoxy, and tert-butoxy)-substituted carbonyl groups, specifically, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 2-propoxycarbonyl, or tert-butoxycarbonyl.

Examples of substituents for “optionally substituted alkoxycarbonyl groups” include: (a) hydroxyl groups,

- (b) carboxy groups,
- (c) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₆ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),
- (d) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),
- (e) alkyl group- (such as methyl, ethyl, propyl, 2-propyl, butyl, or tert-butyl)-substituted carbonyloxy groups (specifically, methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, 2-propylcarbonyloxy, butylcarbonyloxy, or tert-butylcarbonyloxy),
- (f) alkoxy carbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, 2-propoxy, butoxy, or tert-butoxy)-substituted carbonyl groups; specifically, methoxycarbonyl or ethoxycarbonyl),
- (g) alkyl group- (such as methyl, ethyl, propyl, 2-propyl, butyl, or tert-butyl)-substituted amino groups,
- (h) alkyl group- (such as methyl, ethyl, propyl, 2-propyl, butyl, or tert-butyl)-substituted carbamoyl groups,
- (i) alkyl group- (such as methyl, ethyl, propyl, 2-propyl, butyl, or tert-butyl)-substituted sulfamoyl groups,
- (j) alkyl group- (such as methyl, ethyl, propyl, 2-propyl, butyl, or tert-butyl)-substituted ureido groups,
- (k) alkyloxy carbonyloxy groups (such as C₁ to C₄ alkyloxy- (such as methoxy, ethoxy, propoxy, 2-propoxy, butoxy, or tert-butoxy)-substituted carbonyloxy groups; specifically,

methoxycarbonyloxy, ethoxycarbonyloxy, 2-propoxycarbonyloxy, or tert-butyloxy carbonyloxy),

(l) cycloalkyloxy carbonyloxy groups (such as C₃ to C₁₀ cycloalkyloxy group- (such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, adamantyloxy, or norbornyloxy)-substituted carbonyloxy groups; specifically, cyclopentyloxy carbonyloxy, cyclohexyloxy carbonyloxy, or cycloheptyloxy carbonyloxy), (m) phenyl,

(n) 5-methyl-2-oxo-1,3-dioxolen-4-yl,

(o) 5-oxo-2-tetrahydrofuran-yl,

(p) 1,3-dihydro-3-oxo-1-isobenzofuran-yl,

(q) tetrahydrofuran-yl,

(r) nitrogen-bearing saturated heterocyclic groups (such as pyrrolidinyl, piperidinyl, or morpholinyl),

or (s) halogen atoms (such as fluorine, chlorine, bromine, or iodine atoms).

(9) Examples of substituents for "optionally substituted carbamoyl groups" include alkyl groups (such as linear or branched C₁ to C₄ alkyl groups, specifically, methyl, ethyl, propyl, 2-propyl, or butyl). Also, two substituents of the carbamoyl groups may bond to form an optionally carbon-, nitrogen-, or oxygen-bearing aliphatic heterocycle, such as pyrrolidine (the pyrrolidine may be substituted with a hydroxyl group), piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, or piperazine (the piperazine nitrogen atom may be substituted with methyl or ethyl). Specific examples of "optionally substituted carbamoyl groups" include carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, methylpropylcarbamoyl, cyclopropylcarbamoyl,

cyclopropylmethylcarbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, and morpholinocarbonyl.

(10) Examples of cycloalkyl groups for “optionally substituted cycloalkyl groups” include C_3 to C_{10} cycloalkyl groups, specifically, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and norbornyl.

Examples of substituents for “optionally substituted cycloalkyl groups” include alkyl groups (such as methyl, ethyl, propyl, 2-propyl, butyl, and tert-butyl), aralkyl groups (such as benzyl, 2-phenylethyl, and 1-naphthylmethyl), and fluorine atoms.

(11) Examples of aryl groups for “optionally substituted aryl groups” include C_6 to C_{10} aryl groups, specifically, phenyl, 1-naphthyl, and 2-naphthyl.

Examples of substituents for “optionally substituted aryl groups” include:

- (a) hydroxyl groups,
- (b) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (c) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
- (d) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C_1

to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(e) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(f) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(g) phenyl groups optionally substituted with (aa), (bb), or (cc) below:

(aa) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy),

(bb) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl),

(cc) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),

(h) cyano groups,

(i) carboxy groups,

(j) alkoxy-carbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy,

propoxy, or butoxy)-substituted carbonyl groups, specifically, methoxycarbonyl or ethoxycarbonyl),

(k) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl),

(l) alkylsulfonyl groups (such as methylsulfonyl),

(m) methylenedioxy,

(n) ethylenedioxy,

or (o) phenyloxy groups.

(12) Examples of aryloxy groups for “optionally substituted aryloxy groups” include C_6 to C_{10} aryloxy groups, specifically, phenoxy, 1-naphthyloxy, and 2-naphthyloxy.

Examples of substituents for “optionally substituted aryloxy groups” include those given as examples of substituents for “optionally substituted aryl groups” in (11).

(13) Examples of arylsulfonyl groups for “optionally substituted arylsulfonyl groups” include C_6 to C_{10} arylsulfonyl groups, specifically, benzenesulfonyl, toluenesulfonyl, and naphthalenesulfonyl.

Examples of substituents for “optionally substituted arylsulfonyl groups” include those given as examples of substituents for “optionally substituted aryl groups” in (11).

(14) Examples of alkylsulfonyl groups for “alkylsulfonyl group” include C_1 to C_6 alkylsulfonyl groups, specifically, methylsulfonyl, ethylsulfonyl, propylsulfonyl, 2-propylsulfonyl, butylsulfonyl, pentylsulfonyl, or hexylsulfonyl.

(15) Examples of aralkylsulfonyl groups for “optionally substituted aralkylsulfonyl groups” include the “optionally substituted arylsulfonyl groups” of (13) above bonded to optionally substituted alkylene chains (such as methylene, ethylene, and propylene;

examples of substituents include fluorine atoms, methoxy, ethoxy, propoxy, methyl, ethyl, propyl, or 2-propyl).

(17) Examples of alkoxy groups for “optionally substituted alkoxy groups” include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, and more specifically, methoxy, ethoxy, propoxy, and butoxy.

Examples of substituents for “optionally substituted alkoxy groups” include those given as examples of substituents for “optionally substituted alkoxy carbonyl groups” in (8).

Examples of cycloalkyl groups for the “optionally substituted cycloalkyl groups” of R¹ and R² include C₃ to C₁₀ cycloalkyl groups, specifically, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and norbornyl.

Examples of substituents for the “optionally substituted cycloalkyl groups” of R¹ and R² include those given as examples of substituents for “optionally substituted cycloalkyl groups” as substituents for the “optionally substituted alkyl groups” of R¹ and R² above.

Examples of the “halogen atoms” of R² include fluorine, chlorine, bromine, and iodine atoms.

Examples of cycloalkyloxy groups for the “optionally substituted cycloalkyloxy groups” of R² include C₃ to C₁₀ cycloalkyloxy groups, specifically cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, adamantyloxy, or norbornyloxy.

Examples of substituents for the “optionally substituted cycloalkyloxy groups” of R² include those given as examples of substituents for “optionally substituted cycloalkyl groups” as substituents for the “optionally substituted alkyl groups” of R¹ and R² above.

Examples of alkenyl groups for the “optionally substituted alkenyl groups” of R² include C₂ to C₆ alkenyl groups, specifically, vinyl, propenyl, methylpropenyl, butenyl,

and methylbutenyl.

Examples of substituents for the "optionally substituted alkenyl groups" of R² include:

- (a) hydroxyl groups,
- (b) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (c) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
- (d) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),
- (e) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),
- (f) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy,

difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(g) phenyl groups optionally substituted with (aa), (bb), or (cc) below:

(aa) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy),

(bb) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl),

(cc) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),

(h) cyano groups,

(i) carboxy groups,

(j) alkoxycarbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, or butoxy)-substituted carbonyl groups, specifically, methoxycarbonyl or ethoxycarbonyl),

(k) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl),

(l) alkylsulfonyl groups (such as methylsulfonyl),

or (m) phenyloxy.

Examples of substituents for the "optionally substituted amino groups" of R² include:

(a) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl,

and butyl),

(b) alkylcarbonyl groups (such as lower alkylcarbonyl groups, specifically C_1 to C_4 alkylcarbonyl groups, and more specifically, acetyl or propionyl),

(c) aroyl groups (such as C_{11} or lower arylcarbonyl groups, specifically benzoyl or naphthoyl),

(d) alkylsulfonyl groups (such as C_1 to C_4 alkylsulfonyl groups, specifically methanesulfonyl or ethanesulfonyl),

(e) arylsulfonyl groups (such as C_{10} or lower arylsulfonyl groups, specifically benzenesulfonyl, toluenesulfonyl, and naphthalenesulfonyl),

(f) optionally substituted aryl groups (such as C_{10} or lower aryl groups, specifically, phenyl, 1-naphthyl, and 2-naphthyl; examples of substituents include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl), alkoxy groups (such as C_1 to C_4 alkoxy groups, specifically, methoxy, ethoxy, propoxy, and butoxy)),

or (g) aralkyl groups (such as benzyl, 2-phenylethyl, or 1-naphthylmethyl).

Examples of optionally substituted amino groups also include (h) imides. Specific examples of "optionally substituted amino groups" include amino, methylamino, ethylamino, dimethylamino, diethylamino, methylethylamino, acetylamino, propionylamino, benzoylamino, naphthoylamino, methylsulfonylamino, ethylsulfonylamino, methylcarbonylamino, ethylcarbonylamino, benzenesulfonylamino,

phthalimide, succinimide, and maleimide.

Examples of substituents for the "optionally substituted carbamoyl groups" of R² include:

a) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),

or aryl groups (such as phenyl, 1-naphthyl, or 2-naphthyl) optionally substituted with (aa), (bb), or (cc) below:

(aa) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),

(bb) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy),

(cc) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl).

Specific examples of "optionally substituted carbamoyl groups" include carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, phenylcarbamoyl, or phenylmethylcarbamoyl.

Two carbamoyl groups may be bonded to form an optionally carbon-, nitrogen-, oxygen-, or sulfur-bearing aliphatic heterocycle, such as pyrrolidine, piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, or piperazine (a nitrogen atom of the piperazine is optionally substituted with methyl, ethyl, or propyl). Specific examples include pyrrolidinocarbamoyl, piperidinocarbamoyl, or morpholinocarbamoyl.

Examples of alkoxy for the “optionally substituted alkoxy groups” of R^2 include lower alkoxy groups, specifically, C_1 to C_4 alkoxy groups, and more specifically, methoxy, ethoxy, propoxy, and butoxy.

Examples of substituents for the “optionally substituted alkoxy groups” of R^2 include those given as examples of substituents for the “optionally substituted alkoxycarbonyl groups” as substituents for the “optionally substituted alkyl groups” of R^1 and R^2 above.

Examples of alkoxycarbonyl for the “optionally substituted alkoxycarbonyl groups” of R^2 include methoxycarbonyl, ethoxycarbonyl, and propoxycarbonyl.

Examples of substituents for the “optionally substituted alkoxycarbonyl groups” of R^2 include those given as examples of substituents for the “optionally substituted alkoxycarbonyl groups” as substituents for the “optionally substituted alkyl groups” of R^1 and R^2 above.

Examples of aryl groups for the “optionally substituted” aryl groups of R^1 and R^2 include C_6 to C_{10} aryl groups, specifically, phenyl, 1-naphthyl, and 2-naphthyl.

Examples of substituents for the “optionally substituted aryl groups” of R^1 and R^2 include:

- (a) hydroxyl groups,
- (b) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (c) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
- (d) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C_1

to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(e) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(f) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, or trifluoromethoxy),

(g) phenyl groups optionally substituted with (aa), (bb), or (cc) below:

(aa) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy),

(bb) optionally halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl),

(cc) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),

(h) cyano groups,

- (i) carboxy groups,
- (j) optionally atom- (such as fluorine, chlorine, bromine, and iodine atom)-substituted alkoxy carbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, and butoxy)-substituted carbonyl groups, specifically, methoxycarbonyl or ethoxycarbonyl)
- (k) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl),
- (l) alkylsulfonyl groups (such as methylsulfonyl),
- (m) methylenedioxy,
- (n) ethylenedioxy,
- (o) optionally substituted phenoxy groups (substituents include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms) and alkoxy groups (such as C₁ to C₄ alkoxy groups, specifically, methoxy, ethoxy, propoxy, or butoxy)),
- (p) phenyl,
- (q) nitrogen-bearing saturated heterocyclic groups (such as pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl (the piperazine nitrogen atom is optionally substituted with, for example, methyl, ethyl, or propyl)),
- (r) cycloalkyloxy groups (examples of cycloalkyloxy groups include lower cycloalkyloxy groups, specifically C₃ to C₁₀ cycloalkyloxy groups (such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, adamantyloxy, or norbornyloxy) optionally substituted with alkyl groups (such as methyl, ethyl, propyl, 2-propyl, or butyl)), halogen atoms (such as fluorine, chlorine, bromine, or iodine atoms),

or alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, butoxy); specifically, 2-methylcyclopropyloxy, 2-fluorocyclopropyloxy, 3-methoxycyclobutyloxy, or 3-fluorocyclobutyloxy),

(s) difluoromethylenedioxy,

(t) alkenyl groups (such as C₂ to C₆ alkenyl groups, specifically, vinyl, propenyl, methylpropenyl, butenyl, or methylbutenyl),

(u) optionally halogen atom- (such as fluorine, chlorine, bromine, or iodine atom)-substituted alkenyl groups (such as C₂ to C₆ alkenyl groups, specifically, vinyl, propenyl, methylpropenyl, butenyl, or methylbutenyl),

(v) optionally alkyl group- (such as methyl, ethyl, or propyl)-substituted amino groups (specifically, amino, methylamino, ethylamino, propylamino, or dimethylamino),

(w) alkylcarbonyl groups (such as lower alkylcarbonyl, specifically C₁ to C₄ alkylcarbonyl groups, more specifically, acetyl or propionyl),

(x) acetoxy,

(y) alkoxy- (such as lower alkoxy group, specifically, C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

or (z) cycloalkyloxy group- (such as lower cycloalkyloxy group, specifically C₃ to C₁₀ cycloalkyloxy group, more specifically cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, adamantyloxy, or norbornyloxy)-substituted alkoxy

groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, cyclopropyloxymethoxy, cyclobutyloxymethoxy, or cyclopropyloxyethoxy).

Examples of aryloxy groups for the “optionally substituted aryloxy groups” of R² include C₆ to C₁₀ aryloxy groups, specifically, phenoxy, 1-naphthyloxy, and 2-naphthyloxy.

Examples of substituents for the “optionally substituted aryloxy groups” of R² include those given as examples of substituents for the “optionally substituted aryl groups” of R¹ and R². In addition to the above, substituents for the “optionally substituted aryloxy groups” of R² also include groups represented by the formula -O-Ty given below.

Examples of aryloxy carbonyl groups for the “optionally substituted aryloxy carbonyl groups” of R² include C₇ to C₁₁ aryloxy carbonyl groups, specifically, phenyloxy carbonyl, 2-naphthyloxy carbonyl, or 1-naphthyloxy carbonyl.

Examples of substituents for the “optionally substituted aryloxy carbonyl groups” of R² include those given as examples of substituents for the “optionally substituted aryl groups” of R¹ and R² above.

Examples of “optionally substituted aralkyl groups” for R² include aryl groups optionally substituted with optionally substituted alkylene chains.

Examples of “aryl” moieties include C₆ to C₁₀ aryl groups, specifically, phenyl or naphthyl. Examples of substituents for the “optionally substituted aryl group” moieties include those given as examples of substituents for the “optionally substituted aryl groups” of R¹ and R² above.

Examples of alkylene chains for “optionally substituted alkylene chains” include C₁ to C₄ alkylene chains, specifically, methylene, ethylene, trimethylene, or tetramethylene. Examples of substituents for the “optionally substituted alkylene chain” moieties include

alkyl groups (such as linear or branched C₁ to C₄ alkyl groups, specifically, methyl, ethyl, propyl, 2-propyl, or butyl) or halogen atoms (such as fluorine, chlorine, bromine, or iodine atoms). There may be one or more substituents. Two alkyl groups on adjacent or the same carbon may also bond, forming C₃ to C₁₀ cycloalkyls (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, or norbornyl).

Examples of aralkyl groups for the “optionally substituted aralkyloxy groups” of R² include the aralkyl groups of the “optionally substituted aralkyl groups” of R², specifically, benzyloxy or 2-phenylethyloxy. Examples of substituents for the “optionally substituted aryl groups” of the “optionally substituted aralkyloxy groups” include those given as examples of substituents for R¹ and R² above.

Examples of aroyl groups for the “optionally substituted aroyl groups” of R² include C₇ to C₁₁ such as, specifically, benzoyl, 1-naphthoyl, or 2-naphthoyl.

Examples of substituents for the “optionally substituted aroyl groups” of R² include those given as examples of substituents for the “optionally substituted aryl groups” of R¹ and R².

Examples of arylthio groups for the “optionally substituted arylthio groups” of R² include C₆ to C₁₀ arylthio groups, specifically, phenylthio, 1-naphthylthio, or 2-naphthylthio.

Examples of substituents for the “optionally substituted arylthio groups” of R² include those given as examples of substituents for the “optionally substituted aryl groups” of R¹ and R² above.

Examples of arylsulfinyl groups for the “optionally substituted arylsulfinyl groups” of R² include C₆ to C₁₀ arylsulfinyl groups, specifically, phenylsulfinyl, 1-naphthylsulfinyl, and 2-naphthylsulfinyl.

Examples of substituents for the “optionally substituted arylsulfinyl groups” of R^2 include those given as examples of substituents for the “optionally substituted aryl groups” of R^1 and R^2 above.

Examples of arylsulfonyl groups for the “optionally substituted arylsulfonyl groups” of R^2 include C_6 to C_{10} arylsulfonyl groups, specifically, phenylsulfonyl, tosyl, 1-naphthylsulfonyl, and 2-naphthyl sulfonyl.

Examples of substituents for the “optionally substituted arylsulfonyl groups” of R^2 include those given as examples of substituents for the “optionally substituted aryl groups” of R^1 and R^2 above.

Examples of alkylthio groups for the “optionally substituted alkylthio groups” of R^2 include C_1 to C_6 alkylthio groups, specifically, methylthio, ethylthio, propylthio, 2-propylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio, and hexylthio.

Examples of substituents for the “optionally substituted alkylthio groups” of R^2 include those given as examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 above.

Examples of the alkylsulfinyl groups for the “optionally substituted alkylsulfinyl groups” of R^2 include C_1 to C_6 alkylsulfinyl groups, specifically, methylsulfinyl, ethylsulfinyl, propylsulfinyl, 2-propylsulfinyl, butylsulfinyl, pentylsulfinyl, and hexylsulfinyl.

Examples of substituents for the “optionally substituted alkylsulfinyl groups” of R^2 include those given as examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 above.

Examples of alkylsulfonyl groups for the “optionally substituted alkylsulfonyl groups” of R^2 include C_1 to C_6 alkylsulfonyl groups, specifically, methylsulfonyl, ethylsulfonyl, propylsulfonyl, 2-propylsulfonyl, butylsulfonyl, pentylsulfonyl, and hexylsulfonyl.

Examples of substituents for the “optionally substituted alkylsulfonyl groups” of R^2 include those given as examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 above.

Examples of heteroaryl groups for the “optionally substituted heteroaryl groups” of R^1 and R^2 include groups of 5- to 6-member monocyclic or polycyclic rings, and preferably 5- to 6-member monocyclic or bicyclic heterocyclic groups, with one or more (such as 1 to 4) hetero atoms selected from nitrogen, sulfur, and oxygen atoms. Specific examples include pyrrolyl, thienyl, benzothienyl, benzofuranyl, benzoxazolyl, benzthiazolyl, furyl, oxazolyl, thiazolyl, isooxazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, triazolyl, triazinyl, tetrazolyl, indolyl, imidazo[1,2-a]pyridyl, and dibenzofuranyl.

Examples of substituents for the “optionally substituted heteroaryl groups” of R^1 and R^2 include:

- (1) hydroxyl groups,
- (2) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (3) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_6 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),
- (4) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically, linear or branched C_1

to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(5) alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(6) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(7) cyano groups,

(8) carboxy groups,

(9) alkoxycarbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, or butoxy)-substituted carbonyl groups; specifically, methoxycarbonyl or ethoxycarbonyl),

(10) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl), or

(11) optionally substituted aryl groups (such as C₁₀ or lower aryl groups, specifically, phenyl, 1-naphthyl, and 2-naphthyl; examples of substituents include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), alkyl groups (such as linear or branched lower alkyl groups, specifically linear or branched C₁ to C₆ alkyl groups, more

specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl), or alkoxy groups (such as C₁ to C₄ alkoxy groups, specifically, alkoxy groups, specifically, methoxy, ethoxy, propoxy, or butoxy)).

Examples of heteroaryl groups for the “optionally substituted heteroarylalkyl groups” of R² include those given as examples of heteroaryl groups for the “optionally substituted heteroaryl groups” of R¹ and R² above.

Examples of substituents for the “optionally substituted heteroarylalkyl groups” of R² include those given as examples of substituents for the “optionally substituted heteroaryl groups” of R¹ and R² above.

Examples of heteroaryl groups for the “optionally substituted heteroarylcarbonyl groups” of R² include those given as examples of heteroaryl groups for the “optionally substituted heteroaryl groups” of R¹ and R² above.

Examples of substituents for the “optionally substituted heteroarylcarbonyl groups” of R² include those given as examples of substituents for the “optionally substituted heteroaryl groups” of R¹ and R² above.

Examples of heteroaryl groups for the “optionally substituted heteroaryloxy groups” of R² include those given as examples of heteroaryl groups for the “optionally substituted heteroaryl groups” of R¹ and R² above.

Examples of substituents for the “optionally substituted heteroaryloxy groups” of R² include those given as examples of substituents for the “optionally substituted heteroaryl groups” of R¹ and R² above. In addition to the above, substituents for the “optionally substituted heteroaryloxy groups” of R² also include groups represented by the formula -O-Ty given below.

Examples of alkylcarbonyl groups for the “optionally substituted alkylcarbonyl

groups” of R^2 include lower alkylcarbonyl groups, specifically, C_1 to C_4 alkylcarbonyl groups, more specifically, acetyl or propionyl.

Examples of substituents for the “optionally substituted alkylcarbonyl groups” of R^2 include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), specifically, trifluoromethylcarbonyl and pentafluoroethylcarbonyl.

Examples of nitrogen-bearing saturated heterocyclic groups for the “optionally substituted nitrogen-bearing saturated heterocyclic groups” of R^2 and R^3 include 5- or 6-member saturated heterocycles that have 1 or 2 nitrogen atoms and that may furthermore have oxygen or sulfur atoms, specifically, pyrrolidinyl, imidazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, hexamethyleniminyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, oxoimidazolidinyl, dioxoimidazolidinyl, oxooxazolidinyl, dioxooxazolidinyl, dioxothiazolidinyl, tetrahydrofuranlyl, and tetrahydropyridinyl.

Examples of substituents for the “optionally substituted nitrogen-bearing saturated heterocyclic groups” of R^2 and R^3 include:

- (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (2) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
- (3) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(4) alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(5) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(6) cyano groups,

or (7) oxo groups.

Examples of alkyl groups for the “optionally substituted alkyl groups” of R³ include those given as examples of alkyl groups for the “optionally substituted alkyl groups” of R¹ and R² above.

Examples of substituents for the “optionally substituted alkyl groups” of R³ include:

(1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),

(2) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl,

2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(3) alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(4) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(5) cyano groups,

(6) carboxy groups,

(7) alkoxycarbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, or butoxy)-substituted carbonyl groups; specifically, methoxycarbonyl or ethoxycarbonyl),

(8) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl), or

(9) alkylsulfonyl groups (such as methanesulfonyl),

or (10) nitrogen-bearing saturated heterocyclic groups (such as 5- or 6-member saturated heterocyclic groups that have 1 or 2 nitrogen atoms and that may furthermore have an

oxygen atom, specifically, pyrrolidinyl, imidazolidinyl, piperidinyl, and morpholinyl).

The “optionally substituted cycloalkyl groups” of R^3 are the same as the “optionally substituted cycloalkyl groups” of R^1 and R^2 above.

Examples of aryl groups for the “optionally substituted aryl groups” of R^3 include C_6 to C_{10} aryl groups, specifically, phenyl, 1-naphthyl, and 2-naphthyl. Phenyl is preferred.

Examples of substituents for the “optionally substituted aryl groups” of R^3 include:

- (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (2) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
- (3) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C_1 to C_4 alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),
- (4) alkoxy groups (such as lower alkoxy groups, specifically C_1 to C_4 alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),
- (5) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy

moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(6) cyano groups,

(7) alkoxycarbonyl groups (such as C₁ to C₄ alkoxy group- (such as methoxy, ethoxy, propoxy, or butoxy)-substituted carbonyl groups, specifically, methoxycarbonyl or ethoxycarbonyl),

(8) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (specifically, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, or diethylcarbamoyl),

(9) optionally alkyl group- (such as methyl, ethyl, or propyl)-substituted amino groups (specifically, methylamino, ethylamino, propylamino, or dimethylamino),

(10) optionally halogen atom- (such as fluorine atom or chlorine atom)-substituted phenyl groups (specifically, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, or 4-chlorophenyl),

(11) cycloalkyl groups optionally substituted with fluorine atoms (specifically, cyclopropyl, 2-fluorocyclopropyl, cyclobutyl, cyclopentyl, adamantyl, or norbornyl),

(12) cycloalkylcarbonyl groups optionally substituted with fluorine atoms (specifically, cyclopropylcarbonyl, 2-fluorocyclopropylcarbonyl, cyclobutylcarbonyl, or cyclopentylcarbonyl),

(13) carboxy groups,

(14) pyrrolidinyl groups,

- (15) piperidyl groups,
- (16) morpholinyl groups,
- (17) piperazinyl,
- (18) methylenedioxy,
- or (19) ethylenedioxy.

Examples of substituents for the “optionally substituted vinyl groups” of R^3 include (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), and (2) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl). Specific examples of substituted vinyl groups include 1-propylene, 2-methyl-1-propylene, and 2-chloro-1-propylene.

Examples of heteroaryl groups for the “optionally substituted heteroaryl groups” of R^3 include those given as examples of heteroaryl groups for the “optionally substituted heteroaryl groups” of R^1 and R^2 above.

Examples of substituents for the “optionally substituted heteroaryl groups” of R^3 include those given as examples of substituents for the “optionally substituted heteroaryl groups” of R^1 and R^2 above.

Examples of “halogen atoms” for R^4 and R^5 include fluorine, chlorine, bromine, and iodine atoms.

Examples of alkoxy groups for the “optionally substituted alkoxy groups” of R^4 and R^5 include lower alkoxy groups, specifically, C_1 to C_4 alkoxy groups, and more specifically, methoxy, ethoxy, propoxy, and butoxy.

Examples of substituents for the “optionally substituted alkoxy groups” of R^4 and R^5 include those given as examples of substituents for the “optionally substituted alkoxy groups” of R^2 above.

Examples of alkyl groups for the “optionally substituted alkyl groups” of R^4 and R^5 include linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4

alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl.

Examples of substituents for the "optionally substituted alkyl groups" of R^4 and R^5 include:

- (1) hydroxyl groups,
- (2) amino groups,
- (3) cyano groups,
- (4) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (5) alkoxy groups (such as methoxy, ethoxy, propoxy, and butoxy),
- (6) amino groups optionally substituted with any of (a), (b), (c), (d), or (e) below:
 - (a) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
 - (b) alkylcarbonyl groups (such as lower alkylcarbonyl groups, specifically C_1 to C_4 alkylcarbonyl groups, and more specifically, acetyl or propionyl),
 - (c) aroyl groups (such as C_{11} or lower arylcarbonyl groups, specifically benzoyl or naphthoyl),
 - (d) alkylsulfonyl groups (such as C_1 to C_4 alkylsulfonyl groups, specifically methanesulfonyl or ethanesulfonyl),
 - (e) arylsulfonyl groups (such as C_{10} or lower arylsulfonyl groups, specifically benzenesulfonyl, toluenesulfonyl, and naphthalenesulfonyl)
(specifically, methylamino, ethylamino, dimethylamino, diethylamino, methylethylamino, acetylamino, propionylamino, benzoylamino, naphthoylamino,

methylsulfonylamino, ethylsulfonylamino or methylcarbonylamino, ethylcarbonylamino, and benzenesulfonylamino),

or (7) nitrogen-bearing saturated heterocyclic groups (such as 5- or 6-member saturated heterocycles that have 1 or 2 nitrogen atoms and that may furthermore have an oxygen atom, specifically, pyrrolidinyl, imidazolidinyl, piperidinyl, and morpholinyl).

Examples of aryl groups for the “optionally substituted aryl groups” of R^4 and R^5 include phenyl, 1-naphthyl, and 2-naphthyl.

Examples of substituents for the “optionally substituted aryl groups” of R^4 and R^5 include:

- (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (2) alkoxy groups (such as methoxy, ethoxy, propoxy, and butoxy),
- or (3) alkyl groups (such as methyl, ethyl, propyl, or 2-propyl).

The “optionally substituted aralkyl groups” of R^4 and R^5 are the same as the “optionally substituted aralkyl groups” for R^2 above.

Examples of substituents for the “optionally substituted amino groups” of R^4 and R^5 include:

- (1) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),
- (2) alkylcarbonyl groups (such as lower alkylcarbonyl groups, specifically C_1 to C_4 alkylcarbonyl groups, and more specifically, acetyl or propionyl),
- (3) aroyl groups (such as C_{11} or lower arylcarbonyl groups, specifically benzoyl or

naphthoyl),

(4) alkylsulfonyl groups (such as C₁ to C₄ alkylsulfonyl groups, specifically methanesulfonyl or ethanesulfonyl),

(5) arylsulfonyl groups (such as C₁₀ or lower arylsulfonyl groups, specifically benzenesulfonyl, toluenesulfonyl, and naphthalenesulfonyl),

or (6) alkoxy carbonylmethyl (the methyl carbon atom may be substituted with 1 or 2 alkyl groups (such as methyl, ethyl, propyl, or 2-propyl), and the 2 alkyl groups on the methyl carbon atom may be bonded to form cyclopropyl, cyclobutyl, or cyclopentyl with the methyl carbon atom).

Examples of alkoxy carbonyl groups for the “optionally substituted alkoxy carbonyl groups” of R⁴ and R⁵ include carbonyl groups substituted with a C₁ to C₄ alkoxy group (such as methoxy, ethoxy, propoxy, or butoxy). Specific examples include methoxy carbonyl and ethoxy carbonyl.

Examples of substituents for the “optionally substituted alkoxy carbonyl groups” of R⁴ and R⁵ include those given as examples of substituents for the “optionally substituted alkoxy carbonyl groups” of R² above.

Specific examples of substituents for the “optionally substituted carbamoyl groups” of R⁴ and R⁵ include alkyl groups (such as linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, and butyl). Specific examples of “optionally substituted carbamoyl groups” include carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, or ethylmethylcarbamoyl.

Two substituents of the carbamoyl groups may bond to form an optionally carbon-, nitrogen-, oxygen-, or sulfur-bearing aliphatic heterocycle, such as pyrrolidine, piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, or

piperazine (a nitrogen atom of the piperazine is optionally substituted with methyl, ethyl, or propyl), specifically, pyrrolidinocarbamoyl, piperidinocarbamoyl, or morpholinocarbamoyl.

When there are 2 of R^4 or R^5 , they may be on the same or different carbon.

Two R^4 or R^5 together representing methylene or ethylene and bonding with two ring-forming carbon atoms to form a new ring means that a spiro ring or bicyclic ring is formed via the same or different carbons.

Examples of “halogen atoms” for R^6 include fluorine, chlorine, bromine, and iodine atoms.

Examples of “alkylthio groups” for R^6 include thio groups substituted with C_1 to C_4 alkyl groups (such as methyl, ethyl, propyl, 2-propyl, or butyl). Specific examples include methylthio, ethylthio, or propylthio.

Examples of “alkylsulfinyl groups” for R^6 include sulfinyl groups substituted with C_1 to C_4 alkyl groups (such as methyl, ethyl, propyl, 2-propyl, or butyl). Specific examples include methylsulfinyl, ethylsulfinyl, and propylsulfinyl.

Examples of “alkylsulfonyl groups” for R^6 include sulfonyl groups substituted with C_1 to C_4 alkyl groups (such as methyl, ethyl, propyl, 2-propyl, or butyl). Specific examples include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

Examples of “alkyl groups” for R^6 include linear or branched lower alkyl groups, specifically C_1 to C_6 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl.

Examples of “haloalkyl groups” for R^6 include alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically C_1 to C_4 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl) substituted with a halogen

atom (such as a fluorine, chlorine, bromine, or iodine atom), specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, or perfluoroethyl.

Examples of “cycloalkyl groups” for R^6 include C_3 to C_{10} cycloalkyl groups, specifically cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, or norbornyl.

Examples of “alkoxy groups” for R^6 include oxo groups substituted with C_1 to C_4 alkyl groups (such as methyl, ethyl, propyl, 2-propyl, or butyl). Specific examples include methoxy, ethoxy, propoxy, and butoxy.

Examples of “haloalkoxy groups” for R^6 include alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C_1 to C_4 alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy) substituted with halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), specifically, fluoromethoxy, difluoromethoxy, and trifluoromethoxy.

Examples of substituents for the “optionally substituted amino groups” of R^6 include alkyl groups (such as linear or branched C_1 to C_4 alkyl groups, specifically, methyl, ethyl, propyl, 2-propyl, and butyl). Specific examples of “optionally substituted amino groups” include amino, methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

Examples of substituents for the “optionally substituted carbamoyl groups” of R^6 include alkyl groups (such as linear or branched C_1 to C_4 alkyl groups, specifically, methyl, ethyl, propyl, 2-propyl, and butyl). Specific examples of “optionally substituted

carbamoyl groups” include carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, or ethylmethylcarbamoyl.

Examples of “alkoxycarbonyl groups” for R^6 include carbonyl groups substituted with C_1 to C_4 alkoxy groups (such as methoxy, ethoxy, propoxy, or butoxy). Specific examples include methoxycarbonyl, ethoxycarbonyl, and 2-propyloxycarbonyl.

Examples of alkylcarbonyl groups for the “optionally substituted alkylcarbonyl groups” of R^6 include lower alkylcarbonyl groups, specifically C_1 to C_4 alkylcarbonyl groups, more specifically, acetyl or propionyl.

Examples of substituents of the “optionally substituted alkylcarbonyl groups” of R^6 include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), specifically, trifluoromethylcarbonyl or pentafluoroethylcarbonyl.

Examples of “cycloalkylcarbonyl groups” for R^6 include carbonyl groups substituted with C_3 to C_{10} cycloalkyl groups (such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). Specific examples include cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, adamantylcarbonyl, and norbornylcarbonyl.

Examples of aryl groups for the “optionally substituted aryl groups” of R^6 include C_6 to C_{10} aryl groups, specifically, phenyl, 1-naphthyl, and 2-naphthyl.

Examples of substituents for the “optionally substituted aryl groups” of R^6 include:

- (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (2) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or

branched C₁ to C₄ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, and butyl),

(3) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(4) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(5) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

(6) cyano groups,

(7) methylenedioxy,

or (8) ethylenedioxy.

Examples of heteroaryl groups for the "optionally substituted heteroaryl groups" of R⁶ include groups of 5- to 6-member monocyclic or polycyclic rings, and preferably 5- to

6-member monocyclic or bicyclic heterocyclic groups, with one or more (such as 1 to 4) hetero atoms selected from nitrogen, sulfur, and oxygen atoms. Specific examples include pyrrolyl, thienyl, benzothienyl, benzofuranyl, benzoxazolyl, benzthiazolyl, furyl, oxazolyl, thiazolyl, and isooxazolyl.

Examples of substituents for "optionally substituted heteroaryl groups" include:

- (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (2) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₆ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),
- (3) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),
- (4) alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),
- (5) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more

specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy), or (6) cyano groups.

Examples of nitrogen-bearing heteroaryls in the "optionally substituted nitrogen-bearing heteroaryl groups" of R^6 include 5- to 6-member groups with 1 or 2 nitrogen atoms, specifically, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, and pyridazinyl.

Examples of substituents for the "optionally substituted nitrogen-bearing heteroaryl groups" of R^6 include:

- (1) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (2) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_6 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),
- (3) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C_1 to C_4 alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_4 alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl; specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, or methoxyethyl),

(4) alkoxy groups (such as lower alkoxy groups, specifically, C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy),

(5) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or alkoxy group- (such as lower alkoxy group, specifically C₁ to C₄ alkoxy group, more specifically, methoxy, ethoxy, propoxy, or butoxy)-substituted alkoxy groups (examples of alkoxy moieties include lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, or butoxy; specifically, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, or ethoxypropoxy),

or (6) cyano groups.

Examples of “C₁ to C₃ alkylenedioxy groups” for R⁶ include methylenedioxy, ethylenedioxy, and propylene dioxy.

Examples of “halogen atoms” for R⁷ include those given as examples of “halogen atoms” for R⁶ above.

Examples of “alkyl groups” for R⁷ include those given as examples of “alkyl groups” for R⁶ above.

Examples of “haloalkyl groups” for R⁷ include those given as examples of “haloalkyl groups” for R⁶ above.

Examples of “cycloalkyl groups” for R⁷ include those given as examples of “cycloalkyl groups” for R⁶ above.

Examples of “alkoxy groups” for R⁷ include those given as examples of “alkoxy groups” for R⁶ above.

Examples of “haloalkoxy groups” for R⁷ include those given as examples of “haloalkoxy groups” for R⁶ above.

Examples of “alkyl groups” for R¹¹ include those given as examples of “alkyl groups” for R⁶ above.

Examples of “alkylene chains” in R_a include methylene, ethylene, and propylene.

Examples of “optionally substituted alkyl groups,” “optionally substituted alkoxy groups,” “optionally substituted aryl groups,” and “optionally substituted aryloxy groups” in R_c are the same as the “optionally substituted alkyl groups,” “optionally substituted alkoxy groups,” “optionally substituted aryl groups,” and “optionally substituted aryloxy groups” respectively of R^1 and R^2 above.

Examples of “halogen atoms” in R^T include fluorine, chlorine, bromine, and iodine atoms.

Examples of alkyl groups for the “optionally substituted alkyl groups” of R^T include linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_6 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl.

Examples of substituents for the “optionally substituted alkyl groups” of R^T include alkoxycarbonyl groups (such as methoxycarbonyl and ethoxycarbonyl).

Examples of alkoxy groups for the “optionally substituted alkoxy groups” of R^T include lower alkoxy groups, specifically C_1 to C_4 alkoxy groups, more specifically, methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

Examples of substituents for the “optionally substituted alkoxy groups” of R^T include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms).

Examples of “alkoxycarbonyl groups” for the “optionally substituted alkoxycarbonyl groups” of R^T include carbonyl groups substituted with C_1 to C_4 alkoxy groups (such as methoxy, ethoxy, propoxy, 2-propoxy, butoxy, and tert-butoxy), specifically,

methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 2-propoxycarbonyl, and tert-butoxycarbonyl.

Examples of substituents for the “optionally substituted alkoxycarbonyl groups” of R^T include cycloalkyl groups (such as C_3 to C_6 cycloalkyl groups, specifically, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl).

Examples of saturated heterocyclic groups for the “saturated heterocyclic groups” of R^T include 5- or 6-member saturated heterocyclic groups that have 1 or 2 oxygen, nitrogen and/or sulfur atoms, specifically, tetrahydrofuryl and tetrahydropyryl.

Examples of substituents for the “optionally substituted carbamoyl groups” of R^T include alkyl groups (such as linear or branched C_1 to C_4 alkyl groups, specifically, methyl, ethyl, propyl, 2-propyl, and butyl). Specific examples of “optionally substituted carbamoyl groups” include carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, or methylpropylcarbamoyl.

Two R^T together representing methylene, ethylene, trimethylene, tetramethylene, or butenylene and bonding with one or two ring-forming carbon atoms to form a new ring means that a spiro ring or bicyclic ring is formed via the same or different carbons.

When R^2 represents -O-TX-O-Ty, the bonding position of phenylene, pyridinediyl, pyrimidinediyl, and thiophenediyl groups as Tx may be any position on an atom permitting such bonding.

Examples of alkyl groups for “optionally substituted alkyl groups” of Ty include linear or branched lower alkyl groups, specifically, linear or branched C_1 to C_6 alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 3-pentyl, or hexyl.

Examples of alkenyl groups for “optionally substituted alkenyl groups” of Ty include C_2 to C_6 alkenyl groups, specifically, vinyl, propenyl, methylpropenyl, butenyl, and

methylbutenyl.

Examples of cycloalkyl groups for "optionally substituted cycloalkyl groups" of Ty include C₃ to C₆ cycloalkyl groups, specifically, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Examples of cycloalkylalkyl groups for "optionally substituted cycloalkylalkyl groups" of Ty include C₁ to C₄ alkyl groups substituted with C₃ to C₆ cycloalkyl groups, specifically, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, and cyclohexylmethyl.

Examples of saturated heterocyclic groups for the "optionally substituted saturated heterocyclic groups" of Ty include 5- or 6-member saturated heterocyclic groups that have 1 or 2 oxygen, nitrogen and/or sulfur atoms, specifically, tetrahydrofuranlyl, tetrahydropyranlyl, dihydrofurnayl, tetrahydrothiopyranlyl, tetrahydrodioxothiopyranlyl, pyrrolidinyl, piperidyl, piperazyl, imidazolidinyl, oxazolidinyl, and thiazolidinyl.

Examples of substituents for "optionally substituted alkyl groups," "optionally substituted alkenyl groups," "optionally substituted cycloalkyl groups," "optionally substituted cycloalkylalkyl groups," and "optionally substituted saturated heterocyclic groups" of Ty include the following:

- (1) hydroxyl groups,
- (2) halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms),
- (3) oxo groups,
- (4) cyano groups,
- (5) carboxy groups,
- (6) alkyl groups (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₆ alkyl groups, and more specifically, methyl, ethyl, propyl, 2-propyl,

butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or hexyl),

(7) alkyl groups (examples of alkyl moieties include linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, or butyl) substituted with halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), alkoxy groups (such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy), hydroxyl groups, carboxy groups, alkoxy carbonyl groups (such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, and tert-butoxycarbonyl), and cycloalkoxy groups (such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy), specifically, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl, methoxymethyl, hydroxymethyl, carboxymethyl, ethoxycarbonyl, and cyclopropoxymethyl,

(8) alkoxy groups (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy),

(9) carbonyl groups substituted with alkoxy carbonyl groups (such as C₁ to C₄ alkoxy groups (such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy); specifically, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, sec-butoxycarbonyl, and tert-butoxycarbonyl),

(10) halogen atom- (such as fluorine, chlorine, bromine, and iodine atom)- or cycloalkyl group- (such as C₃ to C₆ cycloalkyl groups, specifically, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl)-substituted alkoxy carbonyl groups (specifically,

fluoromethoxycarbonyl, difluoromethoxycarbonyl, trifluoromethoxycarbonyl, fluoroethoxycarbonyl, and cyclopropylmethoxycarbonyl),

(11) cycloalkoxycarbonyl groups (such as cyclopropyloxycarbonyl),

(12) saturated heterocyclic group oxycarbonyl groups (such as carbonyl groups substituted with 5- or 6-member saturated heterocyclic group oxy groups with 1 or 2 oxygen, nitrogen and/or sulfur atoms, specifically, tetrahydrofuranyloxycarbonyl or tetrahydropyranyloxycarbonyl),

(13) carbamoyl groups,

(14) optionally alkyl group- (such as methyl, ethyl, propyl, 2-propyl, or butyl)-substituted carbamoyl groups (two substituents of the carbamoyl groups may bond to form an optionally carbon-, nitrogen-, or oxygen-bearing aliphatic heterocycle, such as pyrrolidine, piperidine, or morpholine); specific examples include methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, pyrrolidinocarbonyl, and morpholinocarbonyl),

15) alkyl group- (such as linear or branched lower alkyl groups, specifically, linear or branched C₁ to C₄ alkyl groups, more specifically, methyl, ethyl, propyl, 2-propyl, butyl, isobutyl, sec-butyl, and tert-butyl), cycloalkyl group- (such as C₃ to C₆ cycloalkyl groups, specifically, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or alkoxy group- (such as lower alkoxy groups, specifically C₁ to C₄ alkoxy groups, more specifically, methoxy, ethoxy, propoxy, and butoxy)-substituted sulfonylcarbamoyl groups (specifically, methylsulfonylcarbamoyl, cyclopropylsulfonylcarbamoyl, or methoxysulfonyl carbamoyl),

(16) alkylcarbonyl groups (such as methylcarbonyl),

(17) alkylsulfonyl groups (such as methylsulfonyl),

- (18) cycloalkylidene groups (such as cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene),
(19) tetrahydropyranlydene,
(20) tetrahydropyranlyl,
(21) heteroaryl groups (such as groups of 5- to 6-member monocyclic or polycyclic rings, and preferably 5- to 6-member monocyclic heterocyclic groups, with one or more (such as 1 to 4) hetero atoms selected from nitrogen, sulfur, and oxygen atoms, specifically, pyrrolyl, thienyl, furyl, oxazolyl, thiazolyl, isooxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, triazolyl, triazinyl, and tetrazolyl),
(22) alkylcarbonylamino groups (such as acetylamino),
(23) alkylaminocarbonyloxy groups (such as dimethylaminocarbonyloxy),
or (24) alkoxy carbonylamino groups (such as methoxycarbonylamino).

Preferred examples of R^1 include hydrogen, methyl, and ethyl, and especially methyl.

Preferred examples of R^3 include halogen atom-substituted phenyl groups, especially 2-chlorophenyl. Other preferred examples of R^3 are 2-chloro-5-fluorophenyl, 2-methyl-5-fluorophenyl, 2-methoxy-5-fluorophenyl, and 2-cyano-5-fluorophenyl.

Preferred examples of R^2 include optionally substituted aryloxy groups, optionally substituted heteroaryloxy groups, and groups represented by the Formulas (T1) through (T6), especially substituted phenyl groups and groups represented by the Formulas (T1) through (T6).

Preferred examples of substituents for substituted phenoxy groups include groups

represented by the Formula -O-Ty, especially those substituted at the m-position.

Preferred examples of Ty include substituted alkyl groups, substituted cycloalkyl groups, and optionally substituted cycloalkylalkyl groups.

Examples of preferred substituents for these substituted alkyl groups, substituted cycloalkyl groups, and substituted cycloalkylalkyl groups include halogen atoms (such as fluorine, chlorine, bromine, and iodine atoms), and alkoxy carbonyl groups (such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, sec-butoxycarbonyl, and tert-butoxycarbonyl).

“Prodrugs” include those that are readily hydrolyzed in the body to reproduce the compounds (I) of the present invention, specifically, compounds in which the amino group $-NH_2$ of the compounds represented by Formula (I) are derived from $-NHQ$. Here, Q means the following.

(1)



(2) $-COR^{17}$

(3) $-COO-CR^{18}(R^{19})-OCOR^{20}$

(4) $-COOR^{21}$

(Where R^{17} is a hydrogen atom, C_1 to C_6 alkyl group, or an optionally substituted aryl group such as a phenyl or naphthyl group. R^{18} and R^{19} are each independently a hydrogen atom or a C_1 to C_6 alkyl group. R^{20} is a hydrogen atom, C_1 to C_6 alkyl group, or an aryl group or benzyl group as noted above. R^{21} is a C_1 to C_6 alkyl group or benzyl group.)

Preferred examples of Q include the groups of (1) and (3). Preferred groups of (3) include those in which R^{18} is a hydrogen atom, R^{19} is a hydrogen atom, methyl, or ethyl, and R^{20} is a hydrogen atom, methyl or ethyl. These compounds can be produced in the usual manner (such as Med. Chem. 35, 4727 (1992), WO 01/40180). Prodrugs may also be ones which

change back to the original compound under physiological conditions, as described in "Development of Pharmaceuticals, Vol. 7, Molecular Design," pp. 163-198, Hirokawa Shoten, 1990.

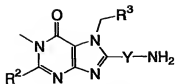
Examples of "pharmaceutically acceptable salts" include inorganic acid salts such as hydrochlorides, hydrobromides, sulfates, phosphates, and nitrates, and organic acid salts such as acetates, propionates, oxalates, succinates, lactates, malates, tartrates, citrates, maleates, fumarates, methanesulfonates, benzenesulfonates, p-toluenesulfonates, and ascorbates.

The present invention also includes hydrates and solvates such as ethanol solvates of the compounds represented by Formula (I), prodrugs thereof, and pharmaceutically acceptable salts thereof in the invention. The present invention furthermore encompasses any tautomers of the compounds (I) of the invention, any existing stereoisomers, and those in any crystal form.

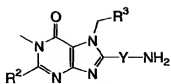
Compounds of the present invention are illustrated by, but are not limited to, the following examples.

No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
1			H	11			CF ₃
2			H	12			CF ₃
3			H	13			CF ₃
4			H	14			CF ₃
5			CH ₃	15			CF ₃
6			CH ₃	16			CF ₃
7			CH ₃	17			CF ₃
8			CH ₃	18			CF ₃
9			CH ₃	19			CF ₃
10			CH ₃	20			CF ₃

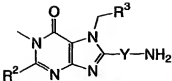








































No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
21			CF ₃	31			NH ₂
22			CF ₃	32			NH ₂
23			CF ₃	33			NH ₂
24			CF ₃	34			N(CH ₃) ₂
25			CF ₃	35			N(CH ₃) ₂
26			CF ₃	36			N(CH ₃) ₂
27			CF ₃	37			N(CH ₃) ₂
28			CF ₃	38			NHC(O)CH ₃
29			CF ₃	39			NHC(O)CH ₃
30			NH ₂	40			NHC(O)CH ₃

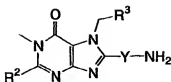


No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
41			NHC(O)CH ₃	51			CH(CH ₃) ₂
42			NHC(O)CH ₃	52			
43			NHS(O) ₂ CH ₃	53			
44			NHS(O) ₂ CH ₃	54			
45			CH ₂ CH ₃	55			OMe
46			CH ₂ CH ₃	56			OMe
47			CH ₂ CH ₃	57			OCF ₃
48			CH ₂ CH ₃	58			OE t
49			CH(CH ₃) ₂	59			OE t
50			CH(CH ₃) ₂	60			OE t

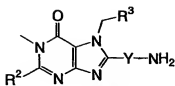


No	R ³	Y-NH ₂	R ²	No	R ³	Y-NH ₂	R ²
61				71			CF ₂ H
62				72			CF ₃ CF ₂
63				73			CF ₃ CH ₂
64				74			CF ₃ CF ₂
65			CF ₃ H	75			CF ₃ CH ₂
66			CF ₃ H	76			CF ₃ CF ₂
67			CF ₃ H	77			CF ₃ CH ₂
68			CF ₃ H	78			CF ₃ CF ₂
69			CF ₃ H	79			CF ₃ CH ₂
70			CF ₃ H	80			CF ₃ CF ₂

							
No	R ³	Y-NH ₂	R ²	No	R ³	Y-NH ₂	R ²
81			CF ₃ CH ₂	91			CF ₃ CF ₂
82			CF ₃ CH ₂	92			CF ₃ CF ₂
83			CF ₃ CF ₂	93			CF ₃ H
84			CF ₃ CH ₂	94			CH ₃ C(0)
85			CF ₃ CF ₂	95			CF ₃ CF ₂
86			CF ₃ CF ₂	96			CN
87			CF ₃ CF ₂	97			CF ₃ CH ₂
88			CF ₃ CF ₂	98			CF ₃
89			CF ₃ CH ₂	99			CN
90			CF ₃ CF ₂	100			CF ₃

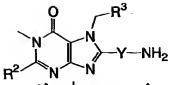










































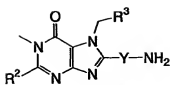
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
101			CF ₃ H	111			CF ₃
102			CF ₃ CH ₃	112			CN
103			CH ₃ C(0)	113			CF ₃ CH ₃
104			CF ₂ H	114			CF ₃ CF ₂
105			CF ₃ CF ₂	115			CF ₃ C(0)
106			CF ₃	116			CF ₃ CF ₂
107			CN	117			CF ₃
108			CH ₃ C(0)	118			CN
109			CF ₂ H	119			CH ₃ C(0)
110			CN	120			CF ₃



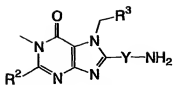
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
121			CF ₃ C(0)	131			CN
122			CH ₃ C(0)	132			CF ₃
123			CF ₂ H	133			CF ₂ H
124			CF ₃ C(0)	134			CF ₃ C(0)
125			CF ₃ CF ₂	135			CF ₂ H
126			CF ₃ CH ₂	136			CF ₂ H
127			CF ₃ CF ₂	137			CF ₃ CF ₂
128			CF ₃ CH ₂	138			CF ₃ CH ₂
129			CF ₃	139			CF ₃ CF ₂
130			CH ₃ C(0)	140			CH ₃ C(0)

No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
141			CF ₃	151			CF ₃ CF ₃
142			CN	152			CH ₃ C(0)
143			CH ₃ C(0)	153			CF ₃ CF ₃
144			CF ₃ C(0)	154			CF ₃ CF ₃
145			CF ₃	155			CF ₃
146			CF ₃	156			CH ₃ C(0)
147			CF ₂ H	157			CN
148			CF ₂ H	158			CF ₃
149			CN	159			CF ₃ C(0)
150			CF ₂ H	160			CN

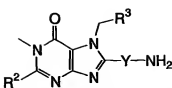




















							
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
161			CF ₂ H	171			CF ₂ H
162			CF ₂ H	172			CF ₂ H
163			CF ₃ CF ₂	173			CF ₃
164			CF ₃ CH ₂	174			CF ₂ H
165			CF ₃ CF ₂	175			CF ₃ CF ₂
166			CF ₃ CH ₂	176			CF ₃ CH ₂
167			CF ₃	177			CF ₃ CH ₂
168			CN	178			CF ₃ CF ₂
169			CH ₃ C(0)	179			CF ₃
170			CF ₃ C(0)	180			CN

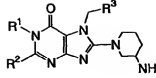










































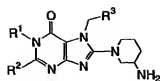
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
181			CH ₃ C (0)	191			CF ₃
182			CF ₃ C (0)	192			CN
183			CF ₂ H	193			CH ₃ C (0)
184			CF ₂ H	194			CF ₃ C (0)
185			CF ₂ H	195			CF ₂ H
186			CF ₂ H	196			CF ₂ H
187			CF ₃ CF ₂	197			CF ₃
188			CF ₃ CH ₂	198			CF ₂ H
189			CF ₃	199			CF ₃ CF ₂
190			CF ₃ CH ₂	200			CF ₃ CH ₂



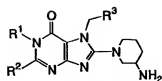
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
201			CF ₃ CF ₂	211			CF ₃ CF ₂
202			CF ₃ CH ₂	212			CF ₃ CF ₂
203			CF ₃	213			CF ₃ CF ₂
204			CN	214			CF ₃ CF ₂
205			CH ₃ C(=O)	215			H
206			CF ₃ C(=O)	216			H
207			CF ₂ H	217			CH ₃
208			CF ₂ H	218			CH ₃
209			CF ₂ H	219			CF ₃
210			CF ₃	220			CF ₃

							
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
221			CF ₃ CF ₂	226			F
222			CF ₃ CF ₂	227			CN
223			CF ₃ CH ₂	228			CN
224			CF ₃ CH ₂	229			CH ₃ C(=O)
225			F	230			CH ₃ C(=O)

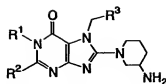
							
No	R ¹	R ²	R ¹	No	R ¹	R ²	R ¹
231		CF ₃		241		CN	
232		CF ₃		242		CF ₃	
233		CF ₃		243		CF ₃	
234		CF ₃		244		CF ₃	
235		CF ₃		245		CF ₃	
236		CF ₃		246		CH ₃ C(O)	
237		CF ₃		247		CF ₃	
238		CH ₃ C(O)		248		CF ₃	
239		CF ₃		249		CF ₃	
240		CF ₃		250		CN	



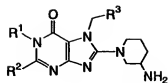
No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
251		CF ₃		261		CF ₃	
252		CN		262		CF ₃	
253		CF ₃		263		CH ₂ C(0)	
254		CF ₃		264		CF ₃	
255		CF ₃		265		CF ₃	
256		CN		266		CF ₃	
257		CF ₃		267		CF ₃	
258		CF ₃		268		CF ₃	
259		CF ₃		269		CF ₃	
260		CH ₂ C(0)		270		CN	



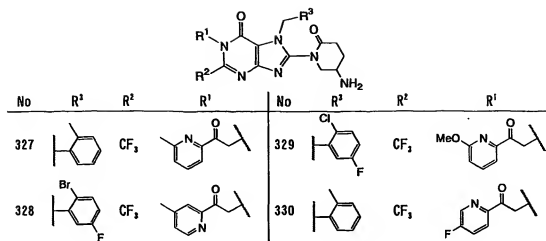
No	R ¹	R ²	R ¹	No	R ¹	R ²	R ¹
271		CF ₃		281		CF ₃	
272		CH ₃ C(O)		282		CN	
273		CF ₃		283		CF ₃	
274		CN		284		CN	
275		CF ₃		285		CF ₃	
276		CF ₃		286		CF ₃	
277		CH ₃ C(O)		287		CH ₃ C(O)	
278		CF ₃		288		CF ₃	
279		CF ₃		289		CF ₃	
280		CF ₃		290		CF ₃	

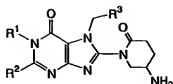


No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
291		CN		301		CH ₃ C(O)	
292		CF ₃		302		CF ₃	
293		CF ₃		303		CF ₃	
294		CH ₃ C(O)		304		CF ₃	
295		CF ₃		305		CF ₃	
296		CF ₃		306		CF ₃	
297		CF ₃		307		CF ₃	
298		CF ₃		308		CF ₃	
299		CF ₃		309		CH ₃ C(O)	CH ₃
300		CN		310		CH ₃ C(O)	CH ₃

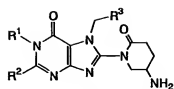


No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
311		CH ₃ C(0)	CH ₃	319		CH ₃ C(0)	
312		CF ₃ C(0)	CH ₃	320		CH ₃ C(0)	
313		CF ₃ C(0)	CH ₃	321		CH ₃ C(0)	
314		CF ₃ C(0)	CH ₃	322		CH ₃ C(0)	
315		CH ₃ CH ₂ C(0)	CH ₃	323		CH ₃ C(0)	
316		CH ₃ CH ₂ C(0)	CH ₃	324		CH ₃ C(0)	
317		CH ₃ CH ₂ C(0)	CH ₃	325		CH ₃ C(0)	
318		CH ₃ C(0)		326		CH ₃ C(0)	

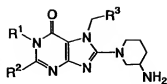




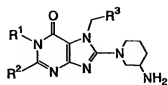
No	R ²	R ¹	No	R ²	R ¹
331		CF ₃	341		CH ₃
332		CF ₃	342		
333		CH ₃ C(0)	343		
334		CH ₃ C(0)	344		
335		CH ₃ C(0)	345		
336		CF ₃ C(0)	346		
337		CF ₃ C(0)	347		
338		CF ₃ C(0)	348		
339		CH ₃ CH ₂ C(0)	349		
340		CH ₃ CH ₂ C(0)	350		



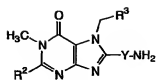
No	R ¹	R ²	R ¹	No	R ¹	R ²	R ¹
351		F		360		CN	
352		F		361		CN	
353		F		362		H	
354		F		363		H	
355		F		364		H	
356		F		365		H	
357		CN		366		CH ₃	
358		CN		367		CH ₃	
359		CN		368		CH ₃	
				369		CH ₃	



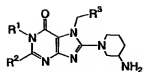
No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
370		CF ₃		379		F	
371		CF ₃		380		F	
372		F		381		F	
373		F		382		F	
374		F		383		F	
375		F		384		F	
376		F		385		CN	
377		F		386		CN	
378		F		387		CN	



No	R ¹	R ²	R ¹	No	R ³	R ²	R ¹
388		CN		393		CN	
389		CN		394		CN	
390		CN		395		CN	
391		CN		396		CN	
392		CN		397		CN	

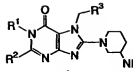




























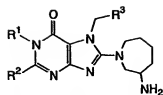
No	R ¹	Y-NH ₂	R ²	No	R ¹	Y-NH ₂	R ²
398			CF ₃	407			CN
399			CF ₃	408			CH ₃ C(0)
400			CF ₃	409			CN
401			CF ₃	410			CN
402			CF ₃	411			CN
403			CF ₃	412			CN
404			CH ₃ C(0)	413			CN
405			CN	414			CN
406			CF ₃ C(0)	415			CN



No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
416		CF ₃	CH ₃	426		CH ₃ C(=O)	
417		CF ₃		427		CF ₃ C(=O)	
418		F		428		CF ₃	
419		CN		429		CF ₃	
420		CF ₃		430		CF ₃	
421		CH ₃ C(=O)		431		CF ₃	
422		CN		432		CF ₃	
423		CH ₃ C(=O)		433		CF ₃	
424		CN		434		CF ₃	CH ₃
425		CF ₃		435		CF ₃	CH ₃

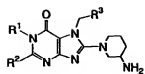
No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
436		CF ₃		446		CH ₃ C (O)	CH ₃
437		CF ₃		447		CN	CH ₃
438		CF ₃		448		CH ₃ C (O)	
439		CF ₃		449		CF ₃	
440		CN		450		CH ₃ C (O)	
441		CN		451		CN	
442		CH ₃ C (O)		452		CF ₃	
443		CH ₃ C (O)		453		CN	
444		CH ₃ C (O)		454		CH ₃ C (O)	
445		CN		455		CF ₃	

							
No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
456		CH ₃ C (O)		463		CN	
457		CN		464		CH ₃ C (O)	
458		CH ₃ C (O)		465		CF ₃	
459		CF ₃		466		CH ₃ C (O)	
460		CH ₃ C (O)		467		CN	
461		CN		468		CH ₃ C (O)	
462		CF ₃					



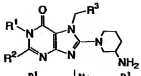
No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
469		CH ₃ C(O)	CH ₃	475		CF ₃	
470		CN	CH ₃	476		CN	
471		CH ₃ C(O)		477		CH ₃ C(O)	
472		CF ₃		478		CF ₃	
473		CH ₃ C(O)		479		CH ₃ C(O)	
474		CN		480		CN	

No	R ¹	R ²	No	R ¹	R ²
481		CF ₃	487		CH ₃ C(0)
482		CN	488		CF ₃
483		CH ₃ C(0)	489		CH ₃ C(0)
484		CN	490		CN
485		CF ₃	491		CF ₃
486		CN			



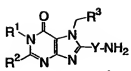




























No	R ¹	R ²	R ³	No	R ¹	R ²	R ³
492			CH ₃	504			CH ₃
493			CH ₃	505			CH ₃
494			CH ₃	506			
495				507			CH ₃
496			CH ₃	508			CH ₃
497			CH ₃	509			CH ₃
498			CH ₃	510			CH ₃
499			CH ₃	511			CH ₃
500			CH ₃	512			CH ₃
501			CH ₃	513			CH ₃
502			CH ₃	514			
503			CH ₃	515			CH ₃

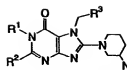
No	R ³	R ²	R ¹	No	R ³	R ²	R ¹
516				526			
517				527			
518			CH ₃	528			CH ₃
519			CH ₃	529			
520			CH ₃	530			CH ₃
521			CH ₃	531			CH ₃
522			CH ₃	532			
523				533			
524			CH ₃	534			
525			CH ₃	535			

							
No	R ¹	R ²	R ³	No	R ¹	R ²	R ³
536			CH ₃	546			
537			CH ₃	547			CH ₃
538			CH ₃	548			
539				549			
540				550			CH ₃
541			CH ₃	551			
542			CH ₃	552			CH ₃ OC(O)CH ₃
543			CH ₃	553			CH ₃
544			CH ₃	554			
545			CH ₃	555			

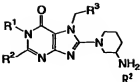

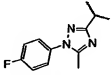

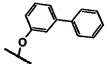
















No	R ²	R ²	R ¹
556			
557			
558			CH ₃
559			CH ₃
560			CH ₃
561			
562			
563			CH ₃
564			CH ₃
565			CH ₃
No	R ²	R ²	R ¹
566			CH ₃
567			CH ₃
568			
569			CH ₃
570			CH ₃
571			
572			CH ₃ OC(O)CH ₃
573			CH ₃
574			
575			CH ₃

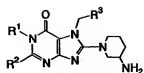
No	R ²	Y-NH ₂	R ²	R ¹
576				CH ₃
577				CH ₃ OC(0)CH ₂
578				
579			CH ₃ CH ₂ OC(0)	
580			CH ₃ OC(0)	
581			CH ₃ CH ₂ OC(0)	CH ₃
582			CH ₃ OC(0)	CH ₃
583			CH ₃ CH ₂ OC(0)	
584			CH ₃ OC(0)	
585			CH ₃ CH ₂ OC(0)	
586			CH ₃ OC(0)	

				
No	R ¹	Y-NH ₂	R ²	R ³
587			CH ₃ CH ₂ OC(O)	
588			CH ₃ OC(O)	
589			CH ₃ CH ₂ OC(O)	
590			CH ₃ OC(O)	CH ₃
591			CH ₃ CH ₂ OC(O)	
592			CH ₃ OC(O)	
593			(CH ₃) ₂ CHCH ₂ OC(O)	CH ₃
594			CH ₃ OC(O)	H
595			CH ₃ OC(O)	H
596			(CH ₃) ₂ CHCH ₂ OC(O)	H
597				H



No	R ¹	R ²	R ³	No	R ¹	R ²	R ³
598			CH ₃	609			CH ₃
599			CH ₃	610			CH ₃
600			CH ₃	611			CH ₃
601			CH ₃	612			CH ₃
602			CH ₃	613			CH ₃
603			CH ₃	614			CH ₃
604			CH ₃	615			CH ₃
605			CH ₃	616			CH ₃
606			CH ₃	617			CH ₃
607			CH ₃	618			CH ₃

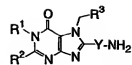









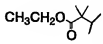







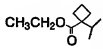














			
No	R ¹	R ²	R ¹
619			CH ₃
620			CH ₃
621			CH ₃
622			CH ₃
623			CH ₃
624			CH ₃
625			CH ₃
626			CH ₃
627			CH ₃
628			CH ₃



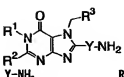






























No	R ¹	R ²	R ¹	No	R ¹	R ²	R ¹
629			CH ₃	641			CH ₃
630			CH ₃	642			CH ₃
631			CH ₃	643			CH ₃
632			CH ₃	644			CH ₃
633			CH ₃	645			CH ₃
634			CH ₃	646			CH ₃
635			CH ₃ OC(O)CH ₂	647			CH ₃ OC(O)CH ₂
636			CH ₃	648			CH ₃
637			CH ₃	649			CH ₃
638			CH ₃	650			CH ₃
639			CH ₃ OC(O)CH ₂	651			CH ₃
640			CH ₃				

No	R ¹	R ²	R ¹	No	R ²	R ¹
652			CH ₃	664		
653				665		CH ₃
654				666		CH ₃
655			CH ₃	667		
656			CH ₃ OC(O)CH ₂	668		CH ₃
657			CH ₃	669		CH ₃
658			CH ₃	670		CH ₃
659		CH ₃ O	CH ₃	671		
660		CH ₃ O	CH ₃ OC(O)CH ₂	672		
661		(CH ₃) ₂ CHO	CH ₃	673		CH ₃
662		(CH ₃) ₂ CHO		674		
663		(CH ₃) ₃ CO	CH ₃			

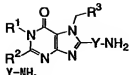












































No	R ²	Y-NH ₂	R ³	R ¹
675				CH ₃
676				CH ₃
677				CH ₃
678				CH ₃
679				CH ₃
680				CH ₃
681				CH ₃ OC(O)CH ₂
682				CH ₃ OC(O)CH ₂
683				CH ₃ OC(O)CH ₂
684				(CH ₃) ₂ CHOC(O)CH ₂
685			CH ₃	CH ₃ OC(O)CH ₂
686			CN	CH ₃ OC(O)CH ₂

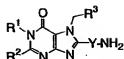
No				
	R ¹	Y-NH ₂	R ²	R ³
687			CF ₃	CH ₃ OC(O)CH ₂
688				
689				
690				
691				
692				
693			CH ₃ OC(O)	H
694			CH ₃ CH ₂ OC(O)	H
695			CH ₃ OC(O)	H
696			CH ₃ CH ₂ OC(O)	H
697			(CH ₃) ₂ CHOC(O)	H

$ \begin{array}{c} \text{R}^1 \\ \text{N} \\ \text{O} \\ \text{R}^2 \quad \text{N} \quad \text{R}^3 \\ \text{Y-NH}_2 \quad \text{Y-NH}_2 \end{array} $				
No	R ¹	Y-NH ₂	R ²	R ³
698				H
699				H
700				H
701				H
702				
703				
704				CH ₃
705				CH ₃
706				CH ₃
707				CH ₃
708				CH ₃
709				CH ₃
710				CH ₃ OC(O)CH ₂

					
No	R ³		R ²		R ¹
711					CH ₃
712			CH ₃ OC(O)		H
713			CH ₃ OC(O)		H
714			CH ₃	CH ₃ OC(O)CH ₂	
715			CF ₃	CH ₃ OC(O)CH ₂	
716			CN	CH ₃ OC(O)CH ₂	
717					CH ₃
718			CN	CH ₃ OC(O)CH ₂	
719			CF ₃	CH ₃ OC(O)CH ₂	
720			CN	CH ₃ CH ₂ OC(O)CH ₂	
721			CF ₃	CH ₃ CH ₂ OC(O)CH ₂	
722					CH ₃
723					CH ₃

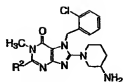
$ \begin{array}{c} \text{R}^1 \text{---} \text{N} \text{---} \text{C}(=\text{O}) \text{---} \text{N} \text{---} \text{R}^3 \\ \text{R}^2 \text{---} \text{N} \text{---} \text{C} \text{---} \text{N} \text{---} \text{Y-NH}_2 \\ \text{Y-NH}_2 \end{array} $				
No	R ¹	R ²	R ³	R ⁴
724				
725				
726				
727				
728			$\text{CH}_3\text{OC(O)}$	
729			CN	
730				
731				
732				
733				
734				
735				
736				

				
No	R ¹	R ²	R ³	R ¹
737				
738			CN	
739				
740				
741			CN	
742			CF ₃	
743				
744				
745			CN	
746			CN	
747			CH ₃ OC(O)	
748			CH ₃ OC(O)	
749			CH ₃ OC(O)	

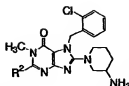


No	R ³	Y-NH ₂	R ²	R ¹
750			CN	
751			CN	
752			CN	
753			CN	
754			CN	
755			CN	
756			CN	
757			CN	
758			CN	
759			CN	
760			CN	
761			CN	
762			CN	

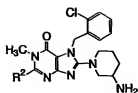
No	R ¹	Y-NH ₂	R ²	R ¹
763			CH ₃ OC(O)	
764				CH ₃ OC(O)CH ₂
765				EtOC(O)CH ₂
766			CH ₃ OC(O)	
767				CH ₃ OC(O)CH ₂
768			CH ₃ OC(O)	
769			CH ₃ OC(O)	
770			CH ₃ OC(O)	
771				CH ₃ OC(O)CH ₂
772				CH ₃ OC(O)CH ₂
773			CH ₃ OC(O)	
774				CH ₃ OC(O)CH ₂
775				



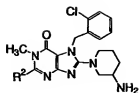
No	R ²	No	R ²	No	R ²
776		784		792	
777		785		793	
778		786		794	
779		787		795	
780		788		796	
781		789		797	
782		790		798	
783		791		799	



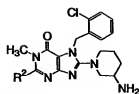
No	R²	No	R²	No	R²
800		808		816	
801		809		817	
802		810		818	
803		811		819	
804		812		820	
805		813		821	
806		814		822	
807		815		823	



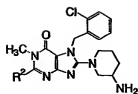
No	R ²	No	R ²	No	R ²
824		832		840	
825		833		841	
826		834		842	
827		835		843	
828		836		844	
829		837		845	
830		838		846	
831		839		847	



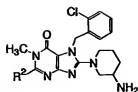
No	R ²	No	R ²	No	R ²
848		856		864	
849		857		865	
850		858		866	
851		859		867	
852		860		868	
853		861		869	
854		862		870	
855		863		871	



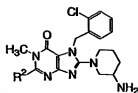
No	R ²	No	R ²	No	R ²
872		880		888	
873		881		889	
874		882		890	
875		883		891	
876		884		892	
877		885		893	
878		886		894	
879		887		895	



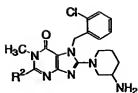
No	R ²	No	R ²	No	R ²
896		904		912	
897		905		913	
898		906		914	
899		907		915	
900		908		916	
901		909		917	
902		910		918	
903		911		919	



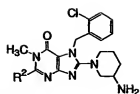
No	R ²	No	R ²	No	R ²
920		928		936	
921		929		937	
922		930		938	
923		931		939	
924		932		940	
925		933		941	
926		934		942	
927		935		943	



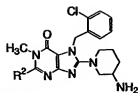
No	R ²	No	R ²	No	R ²
944		952		960	
945		953		961	
946		954		962	
947		955		963	
948		956		964	
949		957		965	
950		958		966	
951		959		967	



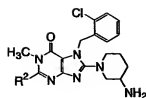
No	R ²	No	R ²	No	R ²
968		976		984	
969		977		985	
970		978		986	
971		979		987	
972		980		988	
973		981		989	
974		982		990	
975		983		991	



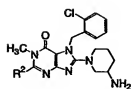
No	R ²	No	R ²	No	R ²
992		1000		1008	
993		1001		1009	
994		1002		1010	
995		1003		1011	
996		1004		1012	
997		1005		1013	
998		1006		1014	
999		1007		1015	



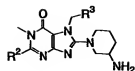
No	R ²	No	R ²	No	R ²
1016		1023		1030	
1017		1024		1031	
1018		1025		1032	
1019		1026		1033	
1020		1027		1034	
1021		1028		1035	
1022		1029		1036	
				1037	



No	R ²	No	R ²
1038		1046	
1039		1047	
1040		1048	
1041		1049	
1042		1050	
1043		1051	
1044		1052	
1045		1053	

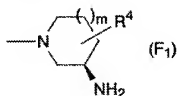


No	R ²	No	R ²
1054		1062	
1055		1063	
1056		1064	
1057		1065	
1058		1066	
1059		1067	
1060		1068	
1061		1069	



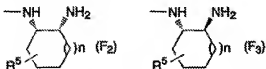
No	R ³	R ²	No	R ³	R ²
1070			1079		
1071			1080		
1072			1081		
1073			1082		
1074			1083		
1075			1084		
1076			1085		
1077			1086		
1078			1087		
			1088		

Compounds in which the amino group in position 3 has an absolute configuration represented by the following Formula (F₁) are more desirable in cases where the portion of the above Compound Nos. 1 to 1088 corresponding to Y-NH₂ in section [1] above is a substituted or unsubstituted 3-aminopyrrolidin-1-yl group, substituted or unsubstituted 3-aminopiperidin-1-yl group, or substituted or unsubstituted (3-amino)hexahydroazepin-1-yl group.



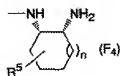
(Where m and R⁴ are defined the same as in item [1] above.)

Compounds in which the groups at positions 1 and 2 have an absolute configuration represented by the following Formulas (F₂) or (F₃) are more desirable in cases where the portions in the above Compound Nos. 1 to 1088 corresponding to Y-NH₂ in section [1] above is a substituted or unsubstituted (2-aminocycloalkyl)amino group,



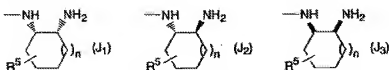
(Where n and R⁵ are defined the same as in section [1])

Compounds in which the amino groups at positions 1 and 2 have an absolute configuration represented by the following Formula (F₄) are even more desirable.



(Where n and R⁵ are defined the same as in section [1])

In the following description, the absolute arrangement of amino groups is represented when bonds are represented by solid-line and broken-line wedges, such as in Formulas (J₁) and (J₂) below, and the relative arrangement of amino groups (for example, (J₃) represents (±)-cis) is represented when bonds are represented by bold lines, such as in Formula (J₃).



(Where n and R⁵ are defined the same as in section [1])

Methods for manufacturing the compounds represented by Formula (I) of the present invention are illustrated by, but are not limited to, the following examples. In this Specification, the following abbreviations are sometimes used for the sake of simplicity.

Boc: tert-butoxycarbonyl group

Cbz: benzyloxycarbonyl group

TBS: tert-butyldimethylsilyl group

Ph: phenyl group

Bn: benzyl group

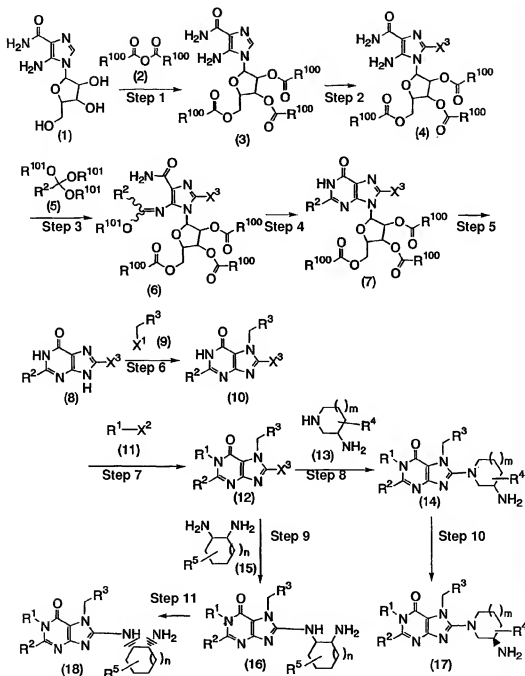
Et: ethyl group

Me: methyl group

The compounds represented by Formula (I) can be synthesized from known compounds by a combination of known synthesis methods. They can be synthesized, for example, by the following methods.

Manufacturing Method 1

Compounds, and their salts, represented by Formulas (14), (17), (16), and (18) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where $R^1, R^2, R^3, R^4, R^5, m$ and n are defined the same as in section [1], X^1 and X^2 are leaving groups (such as bromine atoms, chlorine atoms, methanesulfonyloxy, trifluoromethanesulfonyloxy, or *p*-toluenesulfonyloxy), X^3 is a chlorine or bromine atom,

R¹⁰⁰ is a methyl group, ethyl group, propyl group, 2-propyl group, or phenyl group, and R¹⁰¹ is a methyl group, ethyl group, propyl group, 2-propyl group, benzyl group, or phenyl group.)

1) Step 1

Compound (3) can be produced by a reaction between Compounds (1) and (2) in the presence or absence of additives and the presence of a base in an inert solvent (J. Org. Chem. 39, 3651 (1974), US 3,450,693, etc.). Examples of additives include 4-(dimethylamino)pyridine, and the amount may usually be selected from the range of 0.05 to 0.2 equivalents relative to compound (1). Examples of bases include triethylamine, diisopropylethylamine, tributylamine, 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undeca-7-ene, pyridine, 4-(dimethylamino)pyridine, and picoline. The amount of base may usually be selected from the range of 3 to 10 equivalents relative to compound (1). Examples of inert solvents include aprotic solvents (such as acetonitrile, N,N-dimethyl formamide, and dimethyl sulfoxide), ether-based solvents (such as diethyl ether, tetrahydrofuran, and 1,4-dioxane), ketones (such as acetone), and mixtures of such solvents, and preferably acetonitrile or dimethyl sulfoxide, etc. When compound (2) is a liquid, compound (2) can also be used as the solvent. The amount of compound (2) may usually be selected in the range of 3 to 10 equivalents relative to compound (1). The reaction temperature may be selected from the range of about 10 to about 80°C.

2) Step 2

Compound (4) can be produced by allowing compound (3) to react with N-bromoacetamide or N-chlorosuccinimide in an inert solvent (J. Org. Chem. 39, 3651 (1974), etc.). The amount of the N-bromoacetamide or N-chlorosuccinimide may usually be selected from the range of 1 to 3 equivalents relative to the compound of Formula (3). Examples of inert solvents include aprotic solvents (such as acetonitrile, N,N-dimethyl formamide, and dimethyl sulfoxide), ether-based solvents (such as tetrahydrofuran, 1,4-dioxane and diethyl ether), and mixtures of such solvents, and preferably tetrahydrofuran

or

1,4-dioxane, etc. The reaction temperature may be selected from the range of about -30 to about 50°C.

When X^3 in compound (4) is a bromine atom, compound (3) can be allowed to react with bromine aqueous solution in an aqueous solvent (J. Org. Chem. 33, 1070 (1968), etc.) The bromine aqueous solution may be prepared with a bromine: water volumetric ratio in the range of 0.1:100 to 5:100. The amount of the bromine aqueous solution may usually be selected from the range of 1 to 2 equivalents (molar ratio) relative to the compound of Formula (3). The reaction temperature may be selected from the range of about 10 to about 50°C.

3) Step 3

Compound (6) can be produced by a reaction between compound (4) and compound (5) in the presence of an organic acid in an inert solvent. Examples of inert solvents include aprotic solvents (such as acetonitrile, N,N-dimethyl formamide, and dimethyl sulfoxide), and preferably N,N-dimethyl formamide, etc. Examples of organic acids include acetic acid, propionic acid, and formic acid, and preferably acetic acid, etc. The organic acid can be used as solvent, and the amount may usually be selected from the range of a volumetric ratio of about 0.5 to 1.5 relative to the inert solvent. The reaction temperature may be selected from the range of about 50 to about 150°C. Compound (5) can be a commercially available product or produced by a well known method. Specifically, it can be produced by the method given in "Course in New Experimental Chemistry, Vol. 14: Organic Compound Synthesis and Reaction Solution (II)" (Ed. Chemical Society of Japan, Maruzen).

4) Step 4

Compound (7) can be produced by a reaction between compound (6) and a base in an inert solvent. Examples of bases include potassium tert-butoxide, sodium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, sodium phenoxide, potassium phenoxide, and sodium hydride. The amount of the base may usually be selected from the range of 1 to 5 equivalents relative to compound (6). Examples of inert solvents include tetrahydrofuran, 1,4-dioxane, N,N-dimethyl formamide, and mixtures of such solvents. The reaction temperature may be selected from the range of about 10 to about 50°C.

5) Step 5

Compound (8) can be produced by a reaction between compound (7) and an acid in acetic anhydride. Examples of acids include phosphoric acid, sulfuric acid, and hydrochloric acid, and preferably phosphoric acid, etc. The amount of acid may normally be selected from the range of 0.05 to 10 equivalents relative to compound (7). The reaction temperature may be selected from the range of about 50 to about 130°C.

6) Step 6

Compound (10) can be produced by a reaction between compound (8) and compound (9) in the presence or absence of a base in an inert solvent (J. Heterocycl. Chem. 37, 1033 (2000), J. Chem. Soc., Perkin Trans. 1, 13, 1833 (1999), J. Med. Chem. 38, 3838 (1955), etc.). The amount of compound (9) may normally be selected from the range of 1 to 3 equivalents relative to the compound of Formula (8). Examples of bases include alkali carbonates (such as potassium carbonate, sodium carbonate, potassium bicarbonate, and sodium bicarbonate), alkali hydrides (such as sodium hydride and potassium hydride), and alkali hydroxides (such as potassium hydroxide and sodium hydroxide), and preferably potassium carbonate. The amount of the base may normally be selected from the range of 1 to 5 equivalents relative to compound (8). Examples of inert solvents include aprotic solvents (such as N,N-dimethyl formamide or dimethyl sulfoxide), ether-based solvents (such as diethyl ether, tetrahydrofuran, or 1,4-dioxane), ketones (such as acetone), or mixtures of such solvents, and preferably N,N-dimethyl formamide, dimethyl sulfoxide, etc. The reaction temperature may be selected from the range of about 10 to about 120°C.

By-products in which the R^3CH_2 group is introduced to a different nitrogen atom are commonly produced during the production of Compound (10), but the by-products can be readily eliminated through common methods of purification.

7) Step 7

Compound (12) can be produced by a reaction between compound (10) and compound (11) in the presence of a base in an inert solvent. The amount of compound (11) may normally be selected from the range of 1 to 3 equivalents relative to compound (10). Examples of bases include alkali carbonates (such as potassium carbonate, sodium

carbonate, potassium bicarbonate, and sodium bicarbonate), alkali hydroxides (such as potassium hydroxide and sodium hydroxide), alkali hydrides (such as sodium hydride and potassium hydride), and alkoxyalkalis (such as t-butoxypotassium), and preferably potassium carbonate or sodium carbonate, etc. The amount of the base may normally be selected from the range of 1 to 5 equivalents relative to compound (10). Examples of inert solvents include aprotic solvents (such as N,N-dimethyl formamide or dimethyl sulfoxide), ether-based solvents (such as diethyl ether, tetrahydrofuran, or 1,4-dioxane), ketones (such as acetone), or mixtures of such solvents, and preferably N,N-dimethyl formamide, etc. The reaction temperature may be selected from the range of about 10 to about 100°C.

8) Step 8

Compound (14) can be produced by a reaction between compound (12) and compound (13) in the presence or absence of a base and in the presence or absence of additives in an inert solvent. Examples of additives include 4-(dimethylamino)pyridine. Examples of bases include diisopropylethylamine, triethylamine, pyridine, N-methylmorpholine, or 1-methylpyridine, and preferably diisopropylethylamine or triethylamine, etc. The amount of base may usually be selected from the range of 1 to 10 equivalents relative to compound (12). Examples of inert solvents include alcohol-based solvents (such as ethanol, methanol, and 2-propanol), ether-based solvents (such as 1,4-dioxane), or mixtures of such solvents. The reaction temperature may be selected from the range of about 50 to about 200°C. The reaction can also be carried out in a sealed container such as an autoclave.

Compound (14) in which R¹ is a hydrogen atom can be produced by the same method as above using compound (10) as starting material.

9) Step 9

Compound (16) can be produced by a reaction between compound (12) and compound (15) in the presence or absence of a base and in the presence or absence of additives in an inert solvent. Examples of additives include 4-(dimethylamino)pyridine. Examples of bases include diisopropylethylamine, triethylamine, pyridine, and N-methylmorpholine, and preferably diisopropylethylamine, etc. The amount of base

may usually be selected from the range of 1 to 10 equivalents relative to compound (12). Examples of inert solvents include N-methyl-2-piperidone, N-methyl-2-pyrrolidinone, alcohol-based solvents (such as ethanol, methanol, and 2-propanol), N,N-dimethyl formamide, toluene, or mixtures of such solvents, and preferably N-methyl-2-piperidone and N-methyl-2-pyrrolidinone. The reaction temperature may be selected from the range of about 50 to about 200°C. The reaction can also be carried out in a sealed container such as an autoclave.

Compound (16) in which R¹ is a hydrogen atom can be produced by the same method as above using compound (10) as starting material.

10) Step 10

Compound (17) can be produced by optical resolution of compound (14). As a method of optical resolution, for example, compound (14) can be converted to a salt with an optically active acid (for example, a monocarboxylic acid such as mandelic acid, N-benzyloxyalanine, or lactic acid, a dicarboxylic acid such as tartaric acid, o-isopropylidenetartaric acid, or malic acid, or a sulfonic acid such as camphorsulfonic acid or bromocamphorsulfonic acid) in an inert solvent (for example, alcohol-based solvents such as methanol, ethanol, and 2-propanol, ether-based solvents such as diethyl ether, ester-based solvents such as ethyl acetate, hydrocarbon-based solvents such as toluene, and acetonitrile, or mixtures of such solvents). The temperature for forming the salt may range from room temperature to the boiling point of the solvent. The temperature is preferably increased to around the boiling point of the solvent in order to increase the optical purity. The yield can be increased through cooling as needed before the precipitated salt is filtered off. The amount of optically active acid may normally be selected from the range of about 0.5 to about 2.0 equivalents, and preferably around 1 equivalent, relative to the base. The crystals can be recrystallized as needed in an inert solvent (for example, alcohol-based solvents such as methanol, ethanol, and 2-propanol, ether-based solvents such as diethyl ether, ester-based solvents such as ethyl acetate, hydrocarbon-based solvents such as toluene, and acetonitrile, or mixtures of such solvents), allowing an optical active salt of high purity to be obtained. The resulting salt can be treated with a base in the usual manner as needed to obtain the free form. Compound (14) can also be fractioned using a commercially available chiral column to

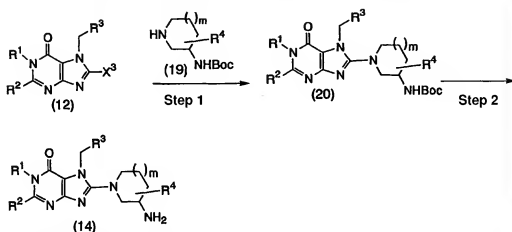
produce compound (17).

11) Step 11

Compound (18) can be produced from compound (16) by the same method as in Step 10 in Manufacturing Method 1 above.

Manufacturing Method 2

Compound (14) can be produced in the following manner when using compound (19) in which the compound (13) amino group in position 3 is protected.



(Where R^1 , R^2 , R^3 , R^4 , and m are defined the same as in section [1], and X^3 is the same as described in Manufacturing Method 1.)

1) Step 1

Compound (20) can be produced from compound (12) in by the same method as in Step 8 of Manufacturing Method 1.

Compound (20) in which R^1 is a hydrogen atom can be produced by the same method as above using compound (10) described in Manufacturing Method 1 as starting material.

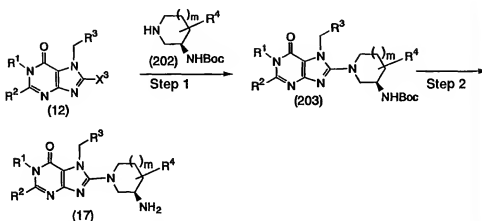
2) Step 2

Compound (14) can be produced by protecting the Boc group of compound (20) in the presence of an acid in an inert solvent. Examples of acids include hydrochloric acid, sulfuric acid, and trifluoroacetic acid, and preferably trifluoroacetic acid, etc. The amount of acid used may normally be selected from the range of 1 to an excess amount relative to compound (20). Examples of inert solvents include halohydrocarbon-based solvents

(such as dichloromethane, dichloroethane, or chloroform), ether-based solvents (such as 1,4-dioxane), or mixtures of such solvents. The reaction temperature may be selected from the range of about -20 to about 30°C.

Manufacturing Method 3

Compound (17) can be produced in the following manner when using compound (202) in which the compound (13) amino group in position 3 is protected.



(Where R¹, R², R³, R⁴, and m are defined the same as in section [1], and X³ is the same as described in Manufacturing Method 1.)

1) Step 1

Compound (203) can be produced from compound (12) by the same method as in Step 8 of Manufacturing Method 1.

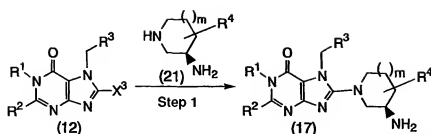
Compound (203) in which R¹ is a hydrogen atom can be produced by the same method as above using compound (10) described in Manufacturing Method 1 as starting material.

2) Step 2

Compound (17) can be produced from compound (203) by the same method as in Step 2 of Manufacturing Method 2.

Manufacturing Method 4

Compound (17) described in Manufacturing Method 1 can be produced in the following manner using optically active compound (21).



(Where R^1 , R^2 , R^3 , R^4 , and m are defined the same as in section [1], and X^3 is the same as described in Manufacturing Method 1.)

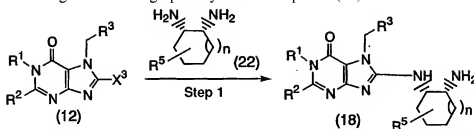
1) Step 1

Compound (17) can be produced from compound (12) by the same method as in Step 8 of Manufacturing Method 1.

Compound (17) in which R^1 is a hydrogen atom can be produced by the same method as above using compound (10) described in Manufacturing Method 1 as starting material.

Manufacturing Method 5

Compound (18) described in Manufacturing Method 1 can be produced in the following manner using optically active compound (22).



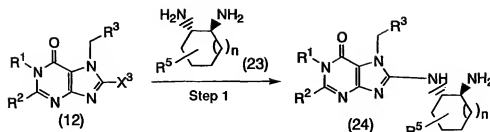
(Where R^1 , R^2 , R^3 , R^5 , and n are defined the same as in section [1], and X^3 is the same as described in Manufacturing Method 1.)

1) Step 1

Compound (18) can be produced from compound (12) by the same method as in Step 9 of Manufacturing Method 1.

Manufacturing Method 6

Compound (24) can be produced in the following manner when using optically active compound (23).



(Where R^1 , R^2 , R^3 , R^5 , and n are defined the same as in section [1], and X^3 is the same as described in Manufacturing Method 1.)

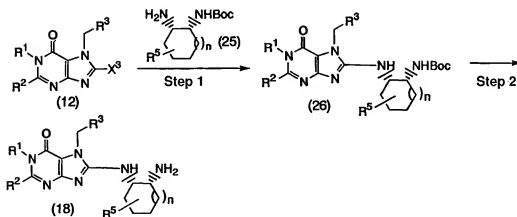
1) Step 1

Compound (24) can be produced from compound (12) by the same method as in Step 9 of Manufacturing Method 1.

Compound (24) in which R^1 is a hydrogen atom can be produced by the same method as above using compound (10) described in Manufacturing Method 1 as starting material.

Manufacturing Method 7

Compound (18) described in Manufacturing Method 1 can be produced in the following manner using optically active compound (25).



(Where R^1 , R^2 , R^3 , R^5 , and n are defined the same as in section [1], and X^3 is the same as described in Manufacturing Method 1.)

1) Step 1

Compound (26) can be produced from compound (12) by the same method as in Step 9 of Manufacturing Method 1.

Compound (26) in which R^1 is a hydrogen atom can be produced by the same method

as above using compound (10) described in Manufacturing Method 1 as starting material.

2) Step 2

Compound (18) can be produced from compound (26) by the same method as in Step 2 of Manufacturing Method 2.

Manufacturing Method 8

Compound (19) can be produced in the following manner, for example.



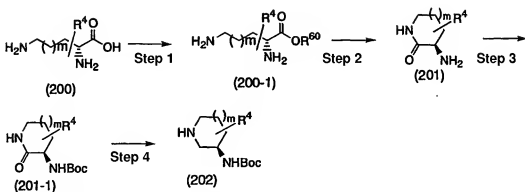
(Where R^4 and m are defined the same as in section [1].)

1) Step 1

Compound (19) can be produced from compound (27) in the same manner as methods of production noted in the literature (such as J. Org. Chem. 58, 879 (1993)).

Manufacturing Method 9

Compound (202) can be produced in the following manner, for example.



(Where R^4 and m are the same as in section [1], and R^{60} is a methyl group or ethyl group.)

1) Step 1

Compound (201) can be produced by allowing compound (200) to react with thionyl chloride in an alcohol-based solvent. Examples of alcohol-based solvent include

methanol and ethanol. The amount of thionyl chloride may normally be selected from the range of 2 to 10 equivalents relative to compound (200). The reaction temperature may be selected from the range of about -90 to about 30°C.

2) Step 2

Compound (201) can be produced by allowing compound (200-1) to react with a base in an aqueous solvent. Examples of bases include sodium bicarbonate, potassium bicarbonate, sodium carbonate, and potassium carbonate. The reaction temperature may be selected from the range of about 30 to about 100°C.

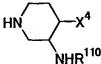
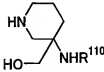


3) Step 3

Compound (201-1) can be produced from compound (201) by the same methods noted in the literature (such as Protective Groups in Organic Synthesis, 2nd Edition (John Wiley & Sons, Inc.)).

4) Step 4

Compound (202) can be produced by allowing compound (201-1) to react with a reducing agent in an inert solvent. Examples of reducing agents include lithium aluminum hydride or diborane. Examples of inert solvents include tetrahydrofuran, 1,4-dioxane, or mixtures of such solvents. The reaction temperature may be selected from the range of about -20 to about 40°C when using lithium aluminum hydride, for example, and the range of about 50 to about 80°C when using diborane.










The synthesis of compounds (13-1A) to (13-4C) is given as a specific example of compound (13). Compounds (13-1A) to (13-4C) include pharmaceutically acceptable salts.

Compound	Manufacturing Method
	WO 02/48138 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
(13-1A): $X^4 = CH_3$	
(13-1B): $X^4 = CH_2CH_3$	
(13-1C): $X^4 = CH_2CH_2OH$	
(13-1D): $X^4 = CH_2CH_2F$	
(13-1E): $X^4 = H$	
	J. Org. Chem. 44, 2732 (1979) J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
(13-2)	
	A method such as that described in J. Org. Chem. 44, 3872 (1979) or J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when compound (13-2) is the starting material
(13-3)	
	Arch. Pharm. 322, 499 (1989) J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
(13-4A): $X^4 = CH_3$	
(13-4B): $X^4 = CH_2CH_3$	
(13-4C): $X^4 = CH_2CH_2CH_3$	

(Where R^{110} is a hydrogen atom, Boc, or Cbz.)





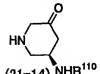
A commercially available product can be used for the hydrochloride of compound (13-1E). Compound (13) can also be synthesized by a well known method from substituted DL-ornithine. Specific examples include the methods noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

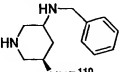



The synthesis of compounds (21-1) to (21-9) is given as specific examples of compound (21). Compounds (21-1) to (21-9) include pharmaceutically acceptable salts.

Compound	Manufacturing Method
 (21-1)	WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-2)	Int. J. Peptide Protein Res. 40, 119 (1992) WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-3)	US 4413141 WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-4)	Tetrahedron: Asymmetry 8, 327 (1997) WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-5)	Tetrahedron: Asymmetry 11, 567 (2000) J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-6)	Chem. Eur. J. 6, 2830 (2000) WO 00/26332 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-7)	Domestic Announcement 2002-525325 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-8)	Bull. Chem. Soc. Jpn. 53, 2605 (1980) J. Chem. Soc., Perkin Trans. 1, 2233 (1999)
 (21-9)	A method such as that described in J. Am. Chem. Soc. 80, 2584 (1958), Chem. Soc PT1 499 (1972), or J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when compound (21-8) is the starting material

(Where R¹¹⁰ is a hydrogen atom, Boc, or Cbz.)


The synthesis of compounds (21-10) to (21-18) is given as specific examples of compound (21). Compounds (21-10) to (21-18) include pharmaceutically acceptable salts.

Compound	Manufacturing Method
 (21-10)	A method such as that described in J. Chem. Soc. Chem. Commun. 611 (1981), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-6) (R ¹¹⁰ is a hydrogen atom)
 (21-11)	A method such as that described in J. Chem. Soc. Chem. Commun. 611 (1981), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-6) (R ¹¹⁰ is a hydrogen atom)
 (21-12)	A method such as that described in J. Org. Chem. 44, 3872 (1979), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-8)
 (21-13)	A method such as that described in J. Org. Chem. 44, 3872 (1979), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-5)
 (21-14)	A method such as that described in Bull. Chem. Soc. Jpn. 64, 2857 (1991), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-8)

Compound	Manufacturing Method
 <p>(21-15)</p>	<p>A method such as that described in Tetrahedron Lett. 40, 5809(1999), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-6) (R¹¹⁰ is a hydrogen atom)</p>
 <p>(21-16A): Y² = (R)-C₆H₅ (21-16B): Y² = (S)-C₆H₅</p>	<p>J. Med. Chem. 35, 833 (1992) "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989, J. Chem. Soc., Perkin Trans. 1, 2233 (1999)</p>
 <p>(21-17A): Y³ = NHS(O)₂CH₃ (21-17B): Y³ = NHC(O)CH₃ (21-17C): Y³ = NHC(O)C₆H₅ (21-17D): Y³ = N(CH₃)C(O)CH₃</p>	<p>A method such as that described in "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989, J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-6) (R¹¹⁰ is a hydrogen atom)</p>
 <p>(21-18)</p>	<p>WO 02/068420 J. Chem. Soc., Perkin Trans. 1, 2233 (1999)</p>

(Where R¹¹⁰ is a hydrogen atom, Boc, or Cbz.)

The synthesis of compounds (21-1A) to (21-1H) is given as specific examples of compound (21). Compounds (21-1A) to (21-1H) include pharmaceutically acceptable salts.

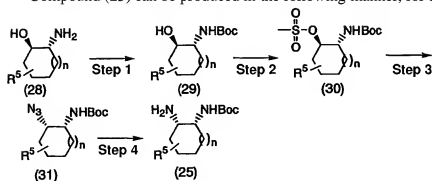
Compound	Manufacturing Method
	<p>A method such as that described in "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989, J. Org. Chem. 68, 3593 (2001), J. Prakt. Chem. 342, 421 (2000), Tetrahedron Lett. 36, 5811 (1994), J. Org. Chem. 53, 5143 (1988), Bioorg. Med. Chem. Lett. 11, 1281 (2001), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) may be used when the starting material is compound (21-14)</p>
(21-1A): Y ⁴ = 2-CH ₃ -C ₆ H ₅	
(21-1B): Y ⁴ = 3-CH ₃ -C ₆ H ₅	
(21-1C): Y ⁴ = 4-CH ₃ -C ₆ H ₅	
(21-1D): Y ⁴ = 2-CH ₃ O-C ₆ H ₅	
(21-1E): Y ⁴ = 3-CH ₃ O-C ₆ H ₅	
(21-1F): Y ⁴ = 4-CH ₃ O-C ₆ H ₅	
(21-1G): Y ⁴ = C ₆ H ₅	
(21-1H): Y ⁴ = CH ₂ C ₆ H ₅	

(Where R¹¹⁰ is a hydrogen atom, Boc, or Cbz.)

Compound (21) can be synthesized from substituted D-ornithine by well known methods. Specific examples are noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

Manufacturing Method 10

Compound (25) can be produced in the following manner, for example.



(Where R⁵ and n is the same as in section [1].)

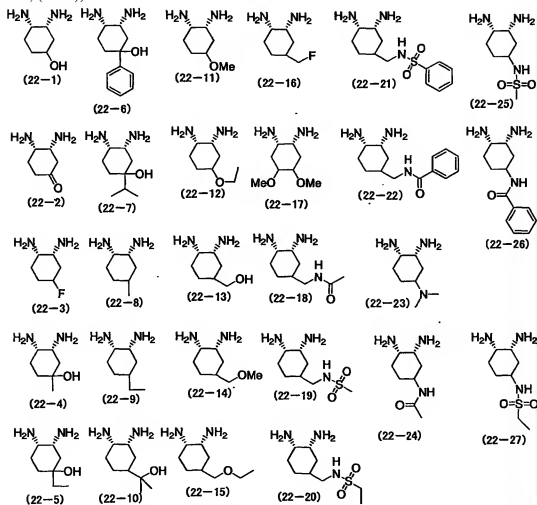
1) Step 1

Compound (29) can be produced from compound (28) by the same methods noted in the literature (such as Protective Groups in Organic Synthesis, 2nd Edition (John Wiley & Sons, Inc.)). Compound (28) can be produced by the same method as noted in J. Org. Chem. 50, 4154 (1985).

2) Steps 2 to 4

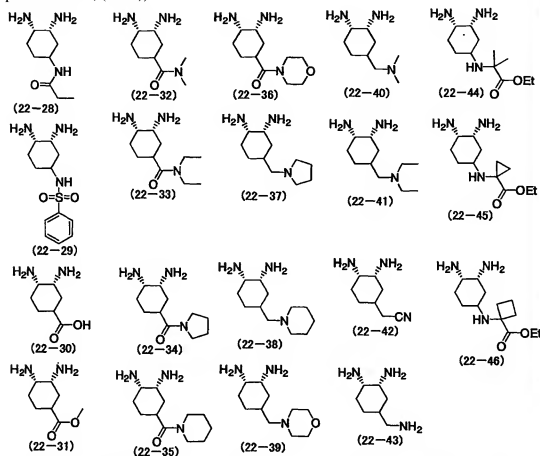
Compound (25) can be synthesized from compound (29) by the same methods as noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

The synthesis of compounds (22-1) to (22-27) is given as specific examples of compound (22). Compounds (22-1) to (22-27) include pharmaceutically acceptable salts. Compounds (22-1) to (22-27) can be produced by methods noted in the literature (such as WO 01/74774 and Comprehensive Organic transformation, R.C. Larock, VCH Publisher Inc., (1989)).



The synthesis of compounds (22-28) to (22-46) is given as specific examples of compound (22). Compounds (22-28) to (22-46) include pharmaceutically acceptable

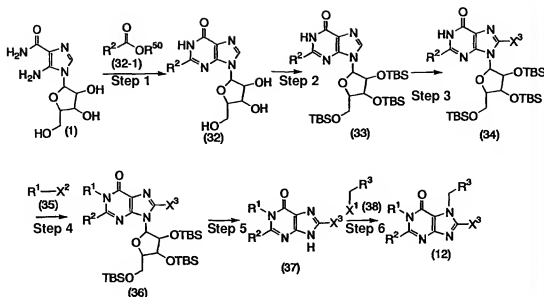
salts. Compounds (22-28) to (22-46) can be produced by methods noted in the literature (such as WO 01/74774 and Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).



Commercially available products can be used for compounds (15) and (23).

Manufacturing Method 11

Compound (12) described in Manufacturing Method 1 can be produced in the following manner, for example.



(Where R¹, R², and R³ are the same as in section [1], X¹, X², and X³ are the same as in Manufacturing Method 1, and R⁵⁰ is a methyl group, ethyl group, propyl group, 2-propyl group, benzyl group, or phenyl group.)

1) Step 1

Compound (32) can be produced by a reaction between compound (1) and compound (32-1) in the presence of a base in an inert solvent. Examples of bases include sodium methoxide and sodium ethoxide. The amount of compound (32-1) may normally be selected from the range of 5 to 30 equivalents relative to compound (1). Examples of inert solvents include ethanol and methanol. The reaction temperature may be selected from the range of about 30 to about 100°C.

2) Step 2

Compound (33) can be produced by a reaction between compound (32) and tert-butyl dimethylsilylchloride in the presence of a base and in the presence or absence of additives in an inert solvent. Examples of additives include 4-(dimethylamino)pyridine, and the amount may usually be selected from the range of 0.05 to 0.5 equivalents relative to compound (32). Examples of bases include imidazole. The amount of base may usually be selected from the range of 3 to 20 equivalents relative to compound (32). The amount of tert-butyl dimethylsilylchloride may normally be selected from the range of 3 to 6

equivalents relative to compound (32). Examples of inert solvents include N,N-dimethyl formamide, tetrahydrofuran, 1,4-dioxane, dichloromethane, or mixtures of such solvents, and preferably N,N-dimethyl formamide. The reaction temperature may be selected from the range of about 10 to about 40°C.

3) Step 3

Compound (34) can be produced by a reaction between compound (33) and a base in an inert solvent, followed by a reaction with a halogenating agent. The amount of base may normally be selected from the range of 2 to 5 equivalents relative to compound (33). The amount of the halogenating agent may normally be selected from the range of 3 to 6 equivalents relative to compound (33). Examples of bases include lithium diisopropylamide, n-butyl lithium, sec-butyl lithium, and tert-butyl lithium; and preferably tert-butyl lithium. Examples of halogenating agents include dibromotetrafluoroethane, diromotetrachloroethane, bromine, N-bromosuccinimide, or N-chlorosuccinimide, and preferably dibromotetrafluoroethane. Examples of inert solvents include tetrahydrofuran, diethyl ether, 1,4-dioxane, or mixtures of such solvents, and preferably tetrahydrofuran. The reaction temperature during the reaction with the base may be selected from the range of about -100 to about 25°C. The reaction temperature can also be increased within that range. The reaction temperature during the reaction with the halogenating agent may be selected from the range of about -10 to about 25°C and may also be increased within that range.

4) Step 4

Compound (36) can be produced from compound (34) in the same manner as in Step 7 of Manufacturing Method 1.

5) Step 5

Compound (37) can be produced from compound (36) in the same manner as in Step 5 of Manufacturing Method 1.

6) Step 6

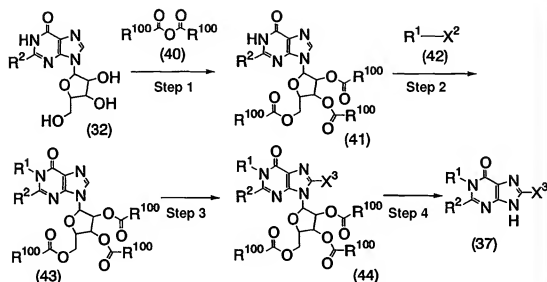
Compound (12) can be produced from compound (37) in the same manner as in Step

6 of Manufacturing Method 1.

By-products in which the R^3 CH_2 group is introduced to a different nitrogen atom are commonly produced during the production of Compound (12), but the by-products can be readily eliminated through common methods of purification, specifically, methods noted in the literature (such as J. Med. Chem., 32, 218 (1989)).

Manufacturing Method 12

Compound (37) of Manufacturing Method 11 can be produced in the following manner, for example.



(Where R^1 and R^2 are the same as in section [1], and X^2 , X^3 , and R^{100} are the same as in Manufacturing Method 1.)

1) Step 1

Compound (41) can be produced from compound (32) in the same manner as in Step 1 of Manufacturing Method 1.

2) Step 2

Compound (43) can be produced from compound (41) in the same manner as in Step 7 of Manufacturing Method 1.

3) Step 3

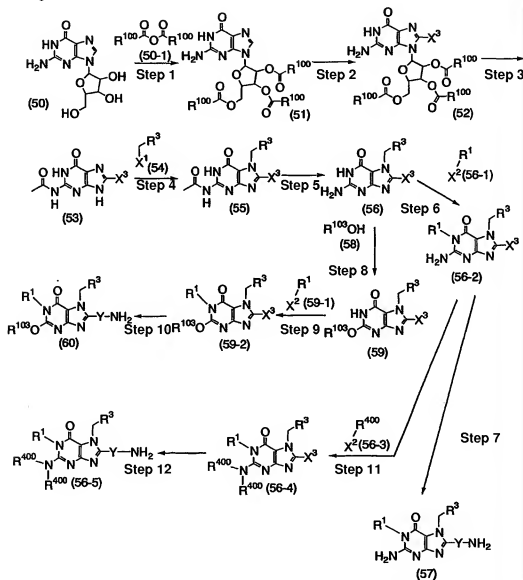
Compound (44) can be produced from compound (43) in the same manner as in Step 2 of Manufacturing Method 1.

4) Step 4

Compound (37) can be produced from compound (44) in the same manner as in Step 5 of Manufacturing Method 1.

Manufacturing Method 13

Compounds, and their salts, represented by Formulas (56-5), (57), and (60) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], R^{100} , X^1 , X^2 , and X^3 are the same as in Manufacturing Method 1, R^{105} represents the "optionally substituted alkoxy

groups” of R^2 in section [1], and R^{100} represents alkyl groups given as examples of substituents for the “optionally substituted amino groups” of R^2 in section [1].)

1) Step 1

Compound (51) can be produced in the same manner as noted in the literature (such as Synthesis 385 (1986)). Compound (50) can also be a commercially available product.

2) Step 2

Compound (52) can be obtained from compound (51) in the same manner as in Step 2 in Manufacturing Method 1.

3) Step 3

Compound (53) can be obtained from compound (52) in the same manner as in Step 5 in Manufacturing Method 1.

4) Step 4

Compound (55) can be produced from compound (53) in the same manner as noted in the literature (such as Synthesis 775 (1999)). By-products in which the $R^3 CH_2$ group is introduced to a different nitrogen atom are commonly produced during the production of Compound (55), but the by-products can be readily eliminated through common methods of purification.

5) Step 5

Compound (56) can be produced by a reaction between compound (55) and inorganic amine in an inert solvent. Examples of organic amines include methylamine, dimethylamine, ethylamine, and diethylamine. The amount of the organic amine may normally be selected from the range of 10 to 200 equivalents relative to compound (55). Examples of inert solvents include alcohol-based solvents such as methanol, ethanol, or 2-propanol, and preferably ethanol. The reaction temperature may be selected from the range of about 0 to about 40°C.

6) Step 6

Compound (56-2) can be produced from compound (56) in the same manner noted in the literature (such as Tetrahedron 58, 3361 (2002), J. Med. Chem., 34, 2380 (1991), Tetrahedron Letters 34, 4595 (1993), J. Org. Chem. 40, 185 (1975), Chem. Ber. 80, 401

(1947), and J. Org. Chem. 41, 568 (1976)).

7) Step 7

Compound (57) can be produced from compound (56-2) in the same manner as in Steps 8 to 11 in Manufacturing Method 1.

Compound (57) in which R¹ is a hydrogen atom can be produced by the same method as above using compound (56) as starting material.

8) Step 8

Compound (59) can be produced by a reaction between compound (56), compound (58), and a nitrite in the presence of an acid. Examples of nitrites include sodium nitrite and potassium nitrite. Examples of acids include sulfuric acid and nitric acid. Compound (58) is usually used as a solvent. The amount nitrite may normally be selected from the range of 2 to 5 equivalents relative to compound (56). The amount of sulfuric acid may be selected from the range of 0.05 to 0.1-fold (volumetric ratio) relative to compound (58). The reaction temperature may be selected from the range of about 50 to about 150°C.

9) Step 9

Compound (59-2) can be produced from compound (59) in the same manner as in Step 7 of Manufacturing Method 1.

10) Step 10

Compound (60) can be produced from compound (59-2) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

Compound (60) in which R¹ is a hydrogen atom can be produced by the same method as above using compound (59) as starting material.

11) Step 11

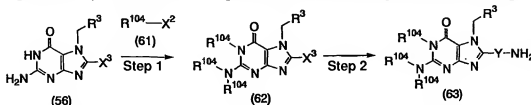
Compound (56-4) can be produced from compound (56-2) in the same manner as in Step 7 of Manufacturing Method 1.

12) Step 12

Compound (56-5) can be produced from compound (56-4) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

Manufacturing Method 14

Compounds, and their salts, represented by Formula (63) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^3 and Y are defined the same as in section [1], X^2 , and X^3 are the same as in Manufacturing Method 1, and R^{104} represents alkyl groups given as examples of substituents for the “optionally substituted amino groups” of R^2 in section [1].)

1) Step 1

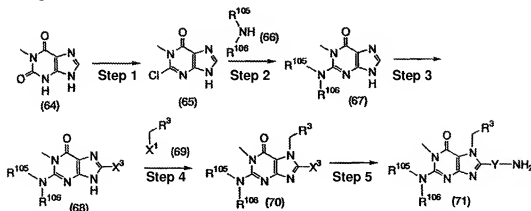
Compound (62) can be produced from compound (56) in the same manner as in Step 7 in Manufacturing Method 1.

2) Step 2

Compound (63) can be produced from compound (62) in the same manner as in Steps 8 to 11 in Manufacturing Method 1.

Manufacturing Method 15

Compounds, and their salts, represented by Formula (71) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^3 and Y are defined the same as in section [1], X^3 is the same as in Manufacturing Method 1, and $R^{105}R^{106}N$ represents the “optionally substituted amino

groups" or "optionally substituted nitrogen-bearing saturated heterocyclic groups" of R² in section [1]).

1) Step 1

Compound (65) can be produced by allowing compound (64) to react with phosphorus oxychloride in an inert solvent as needed in the presence of a base such as dimethylaniline or diethylaniline. Liquid bases can also be used as solvent. The amount of the phosphorus oxychloride may normally be selected from the range of 1 to 5 equivalents relative to compound (64). Examples of inert solvents include ether-based solvents such as tetrahydrofuran or 1,4-dioxane, aprotic solvents such as N,N-dimethyl formamide or dimethyl sulfoxide, hydrocarbon-based solvents such as toluene, benzene, or xylene, halohydrocarbon-based solvents such as dichloromethane, dichloroethane, or chloroform, or mixtures of such solvents, and preferably toluene. The reaction temperature may be selected from the range of about 50 to about 150°C. Commercially available products can also be used for compound (64).

2) Step 2

Compound (67) can be produced by a reaction between compound (65) and compound (66) in the presence of an inorganic base in an inert solvent. Examples of inorganic bases include potassium carbonate and sodium carbonate. Examples of inert solvents include alcohol-based solvents such as methanol, ethanol, and 2-propanol, hydrocarbon-based solvents such as toluene and benzene, aprotic solvents such as N,N-dimethyl formamide and acetonitrile, and ether-based solvents such as tetrahydrofuran or 1,4-dioxane. The reaction temperature may be selected from the range of about 0 to about 150°C.

3) Step 3

Compound (68) can be produced from compound (67) in the same manner as in Step 2 of Manufacturing Method 1.

4) Step 4

Compound (70) can be produced from compound (68) in the same manner as in Step 6 of Manufacturing Method 1. By-products in which the R³ CH₂ group is introduced to a different nitrogen atom are commonly produced during the production of Compound (70),

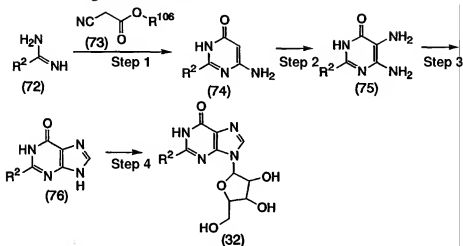
but the by-products can be readily eliminated through common methods of purification.

5) Step 5

Compound (71) can be produced from Compound (70) in the same manner as in Steps 8 to 11 in Manufacturing Method 1.

Manufacturing Method 16

Compound (32) of Manufacturing Method 1 can be produced in accordance with Manufacturing Method 16 below.



(Where R^2 is defined the same as in section [1], and R^{106} is a methyl group, an ethyl group, a propyl group, a 2-propyl group, or a benzyl group.)

1) Steps 1 and 2

Compound (75) can be produced from compound (72) in the same manner noted in the literature (such as J. Org. Chem. 26, 4504 (1961) and US 6,423,720).

2) Step 3

Compound (76) can be produced from compound (75) in the same manner noted in the literature (such as Synthesis 125 (1993)).

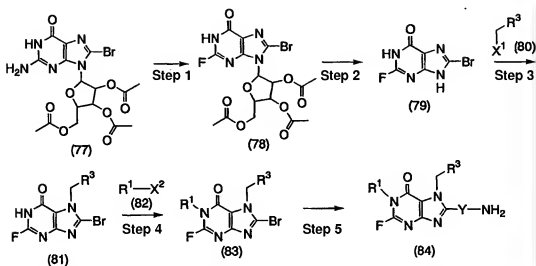
3) Step 4

Compound (32) can be produced from compound (76) in the same manner as noted in the literature (such as J. Org. Chem. 58, 7258 (1993), J. Heterocycl. Chem. 30, 1229

(1993), and Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

Manufacturing Method 17

Compounds, and their salts, represented by Formula (84) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^2 , and Y are defined the same as in section [1], and X^1 and X^2 are the same as in Manufacturing Method 1.)

1) Step 1

Compound (78) can be produced from compound (77) in the same manner noted in the literature (such as Tetrahedron Letters 31, 3019 (1990)). Compound (77) can be produced in the same manner as in Steps 1 and 2 of Manufacturing Method 13 using guanosine as starting material.

2) Step 2

Compound (79) can be produced from compound (78) in the same manner as in Step 5 of Manufacturing Method 1.

3) Step 3

Compound (81) can be produced from compound (79) in the same manner as in Step 6 of Manufacturing Method 1. By-products in which the R^3 CH_2 group is introduced to a different nitrogen atom are commonly produced during the production of Compound (81), but the by-products can be readily eliminated through common methods of purification.

4) Step 4

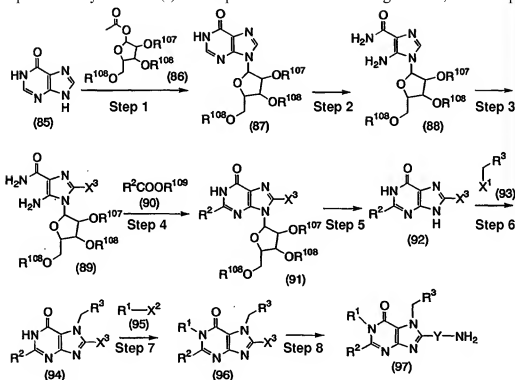
Compound (83) can be produced from compound (81) in the same manner as in Step 7 of Manufacturing Method 1.

5) Step 5

Compound (84) can be produced from compound (83) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

Manufacturing Method 18

Compounds, and their salts, represented by Formula (97) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^2 , R^3 , and Y are defined the same as in section [1], X^1 , X^2 , and X^3 are the same as in Manufacturing Method 1, R^{107} is a methyl group or ethyl group, R^{108} is a benzyl group, methyl group, or ethyl group, and R^{109} is a methyl group or ethyl group.)

1) Step 1

Compound (87) can be produced from compound (85) in the same manner as noted in

the literature (such as J. Med. Chem. 36, 3230 (1993)). Compound (86) can be a commercially available product or produced in the manner noted in the literature (such as Tetrahedron 50, 5361 (1994)).

2) Step 2

Compound (88) can be produced from compound (87) in the same manner as noted in the literature (such as J. Chem. Soc., Perkin Trans. 1, 3489 (1999), Chem. Pharm. Bull. 44, 288 (1996), and Tetrahedron Letters 34, 103 (1993)).

3) Step 3

Compound (89) can be produced from compound (88) in the same manner as in Step 2 of Manufacturing Method 1.

4) Step 4

Compound (91) can be produced from compound (89) in the same manner as noted in the literature (such as Heterocycles 42, 691 (1996)).

5) Step 5

Compound (92) can be produced from compound (91) in the same manner as in Step 5 of Manufacturing Method 1.

6) Step 6

Compound (94) can be produced from compound (92) in the same manner as in Step 6 of Manufacturing Method 1. By-products in which the R^3CH_2 group is introduced to a different nitrogen atom are commonly produced during the production of Compound (94), but the by-products can be readily eliminated through common methods of purification.

7) Step 7

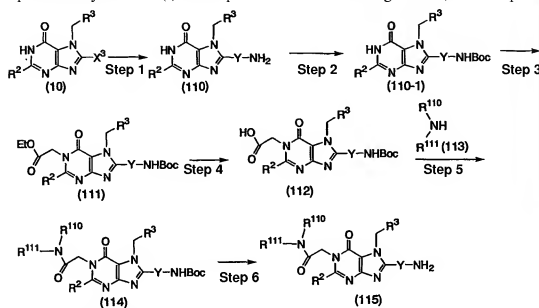
Compound (96) can be produced from compound (94) in the same manner as in Step 7 of Manufacturing Method 1.

8) Step 8

Compound (97) can be produced from compound (96) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

Manufacturing Method 19

Compounds, and their salts, represented by Formula (115) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^2 , R^3 , and Y are defined the same as in section [1], X^3 is the same as in Manufacturing Method 1, and $R^{110}R^{111}NC(O)$ represents the “optionally substituted carbamoyl groups” given as examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 in section [1])

1) Step 1

Compound (110) can be produced from compound (10) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

2) Step 2

Compound (110-1) can be produced from compound (110) in the same manner as in Step 1 of Manufacturing Method 10.

3) Step 3

Compound (111) can be produced from compound (110-1) in the same manner as in Step 7 of Manufacturing Method 1.

4) Step 4

Compound (112) can be produced by hydrolysis of compound (111) in the presence of a base in an inert solvent. Examples of bases include alkali hydroxides (such as sodium hydroxide and potassium hydroxide), which are usually used in the form of aqueous solution. Examples of inert solvents include alcohol-based solvents such as methanol and

ethanol. The reaction temperature may be selected from the range of about 25 to about 80°C.

5) Step 5

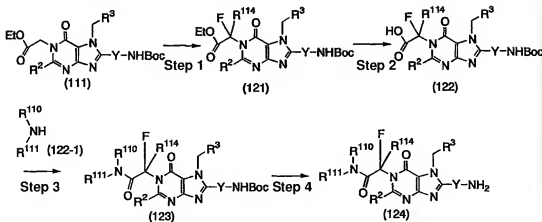
Compound (114) can be produced by condensing compound (112) and compound (113) in the presence of an additive such as 4-(dimethylamino)pyridine as needed using a dehydration condensation agent such as dicyclohexylcarbodiimide or carbonyldiimidazole in an inert solvent. Examples of the inert solvent include ether solvents such as diethyl ether, tetrahydrofuran, and 1,4-dioxane; aprotic solvents such as N,N-dimethylformamide; and halohydrocarbon solvents such as dichloromethane and dichloroethane. Mixtures of these solvents may also be used. A preferable example is N,N-dimethylformamide. The reaction temperature may usually be selected from a range of about 0 to about 50°C.

6) Step 6

Compound (115) can be produced from compound (114) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 20

Compounds, and their salts, represented by Formula (124) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^2 , R^3 , and Y are the same as in section [1], $R^{110}R^{111}NC(O)-$ represents the "optionally substituted carbamoyl groups" given as examples of substituents for the "optionally substituted alkyl groups" of R^1 and R^2 in section [1], and R^{114} is a hydrogen

atom or fluorine atom.)

1) Step 1

Compound (121) can be produced from compound (111) in the same manner as noted in the literature (such as *Angew. Chem.* 108, 1082 (1996), *Bioorg. Med. Chem. Lett.* 8, 3275 (1998), and *Tetrahedron Lett.* 32, 1779 (1991)).

2) Step 2

Compound (122) can be produced from compound (121) in the same manner as in Step 4 of Manufacturing Method 19.

3) Step 3

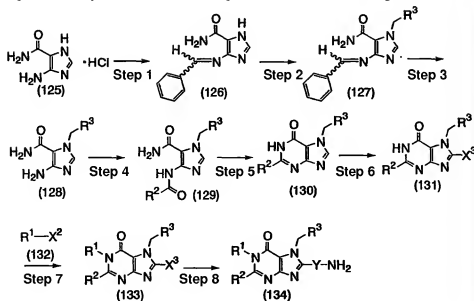
Compound (123) can be produced from compound (122) in the same manner as in Step 5 of Manufacturing Method 19.

4) Step 4

Compound (124) can be produced from compound (123) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 21

Compounds, and their salts, represented by Formula (134) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1, R^2, R^3 , and Y are the same as in section [I], and X^2 and X^3 are the same as in Manufacturing Method 1.)

1) Steps 1 to 5

Compound (130) can be produced from compound (125) by the same methods noted in the literature (such as WO 99/03858).

2) Step 6

Compound (131) can be produced from compound (130) in the same manner as in Step 3 of Manufacturing Method 11. Examples of preferred bases in this step include tert-butyl lithium.

3) Step 7

Compound (133) can be produced from compound (131) in the same manner as in Step 7 of Manufacturing Method 1.

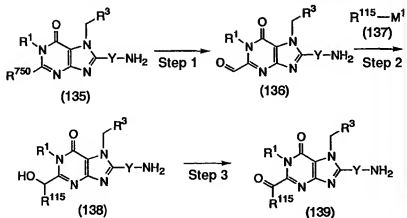
4) Step 8

Compound (134) can be produced from compound (133) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

Compound (134) in which R^1 is a hydrogen atom can be produced by the same method as above using compound (131) as starting material.

Manufacturing Method 22

Compounds, and their salts, represented by Formula (139) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1, R^3 , and Y are the same as in section [I], $R^{115}C(O)$ represents the "optionally

substituted aroyl groups” and “optionally substituted heteroarylcarbonyl groups” of R² in section [I], R⁷⁵⁰ is vinyl or 1-propenyl, and M¹ is lithium, magnesium chloride, or magnesium bromide.)

1) Step 1

Compound (136) can be produced from compound (135) in the same manner as noted in the literature (such as Tetrahedron 45, 3653 (1989)). Compound (135) specifically represents compound (17) or (18) in Manufacturing Method 1, compound (134) in Manufacturing Method 21, compound (142-3) in Manufacturing Method 23, compound (188-5) in Manufacturing Method 29, and compound (228) or (224) in Manufacturing Method 32.

2) Step 2

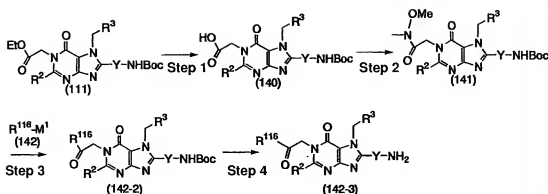
Compound (138) can be produced by a reaction between compound (136) and compound (137) in an inert solvent. The amount of compound (137) may normally be selected from the range of 1 to 5 equivalents relative to compound (136). Examples of inert solvents include tetrahydrofuran, diethyl ether, 1,4-dioxane, or mixtures of such solvents, and preferably tetrahydrofuran. The reaction temperature may be selected from the range of about -100 to about 25°C. Compound (137) can be a commercially available product or produced, for example, by the method noted in Course in Experimental Chemistry (Ed. Chemical Society of Japan, Maruzen), Vol. 25.

3) Step 3

Compound (139) can be produced from compound (138) in the same manner as noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

Manufacturing Method 23

Compounds, and their salts, represented by Formula (142-3) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^2 , R^3 , and Y are the same as in section [1], M^1 is the same as in Manufacturing Method 22, and $R^{116}C(O)$ represents the “optionally substituted aroyl groups” and “optionally substituted nitrogen-bearing heteroarylcarbonyl groups” given as examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 in section [1].)

1) Step 1

Compound (140) can be produced from compound (111) in the same manner as in Step 4 of Manufacturing Method 19.

2) Steps 2 and 3

Compound (142-2) can be produced from compound (140) in the same manner as noted in the literature (such as Bioorg. Med. Chem. Lett. 11, 2951 (2001), Tetrahedron Letters 42, 8955 (2001), Synthesis 1852 (2000), Organic Letters 2, 4091 (2000), Tetrahedron Letters 42, 5609 (2001), Synthesis 2239 (2001), Synlett 5, 715 (2002), J. Org. Chem. 67, 5032 (2002), Bioorg. Med. Chem. Lett. 11, 287 (2001), and Tetrahedron Letters 42, 3763 (2001)). Compound (142) can be a commercially available product or produced by a method noted in the literature such as Course in Experimental Chemistry (Ed. Chemical Society of Japan, Maruzen), Vol. 25.

3) Step 4

Compound (142-3) can be produced from compound (142-2) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 24

Compounds, and their salts, represented by Formula (143) out of the compounds

represented by Formula (I) can be produced in the following manner, for example.



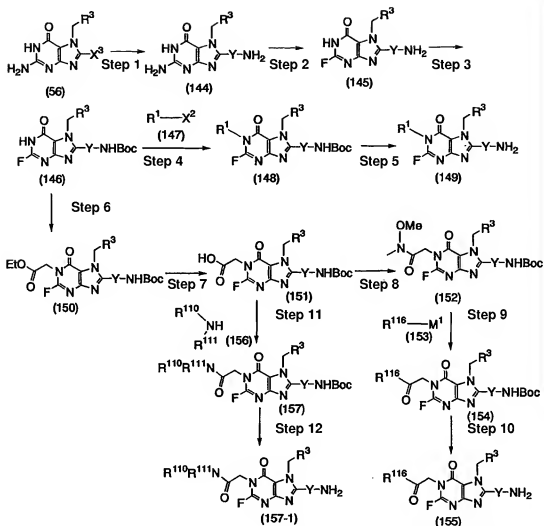
(Where R¹, R³, and Y are the same as in section [1].)

1) Step 1

Compound (143) can be produced from compound (57) in the same manner as noted in the literature (such as *Bioorganic & Medicinal Chemistry* 10, 3555 (2002), *Tetrahedron Lett.* 31, 3019 (1990), *Tetrahedron* 52, 23 (1996), and *Nucleosides, Nucleotides, & Nucleic Acids* 20, 59 (2001)).

Manufacturing Method 25

Compounds, and their salts, represented by Formulas (149), (155), and (157-1) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], X^2 and X^3 are the same as in Manufacturing Method 1, M^1 is the same as in Manufacturing Method 22, $R^{116}C(O)$ is the same as in Manufacturing Method 23, and $R^{110}R^{111}NC(O)$ represents the “optionally substituted carbamoyl groups” and “optionally substituted nitrogen-bearing heteroarylaminocarbonyl groups” given as examples of substituents for the “optionally substituted alkyl groups” of R^1 and R^2 in section [1].)

1) Step 1

Compound (144) can be produced from compound (56) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

2) Step 2

Compound (145) can be produced from compound (144) in the same manner as in

Step 1 of Manufacturing Method 24.

3) Step 3

Compound (146) can be produced from compound (145) in the same manner as in Step 1 of Manufacturing Method 10.

4) Step 4

Compound (148) can be produced from compound (146) in the same manner as in Step 7 of Manufacturing Method 1.

5) Step 5

Compound (149) can be produced from compound (148) in the same manner as in Step 2 of Manufacturing Method 2.

6) Step 6

Compound (150) can be produced from compound (146) in the same manner as in Step 7 of Manufacturing Method 1.

7) Step 7

Compound (151) can be produced from compound (150) in the same manner as in Step 4 of Manufacturing Method 19.

8) Steps 8 and 9

Compound (154) can be produced from compound (151) in the same manner as in Steps 2 and 3 of Manufacturing Method 23.

9) Step 10

Compound (155) can be produced from compound (154) in the same manner as in Step 2 of Manufacturing Method 2.

10) Step 11

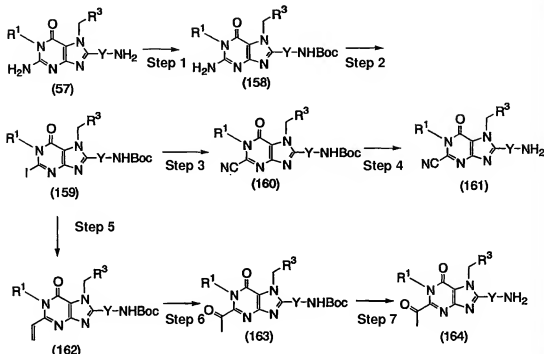
Compound (157) can be produced from compound (151) in the same manner as in Step 5 of Manufacturing Method 19.

11) Step 12

Compound (157-1) can be produced from compound (157) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 26

Compounds, and their salts, represented by Formulas (161) and (164) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1].)

1) Step 1

Compound (158) can be produced from compound (57) in the same manner as in Step 10 of Manufacturing Method 10.

2) Step 2

Compound (159) can be produced from compound (158) in the same manner as noted in the literature (such as Tetrahedron 46, 7677 (1990) and Bioorganic & Medicinal Chemistry 10, 3555 (2002)).

3) Step 3

Compound (160) can be produced from compound (159) in the same manner as noted in the literature (such as Tetrahedron 46, 7677 (1990) and Bioorganic & Medicinal Chemistry 10, 3555 (2002)).

4) Step 4

Compound (161) can be produced from compound (160) in the same manner as in Step 2 of Manufacturing Method 2.

5) Step 5

Compound (162) can be produced from compound (159) in the same manner as noted in the literature (such as Tetrahedron 46, 7677 (1990) and Bioorganic & Medicinal Chemistry 10, 3555 (2002)).

6) Step 6

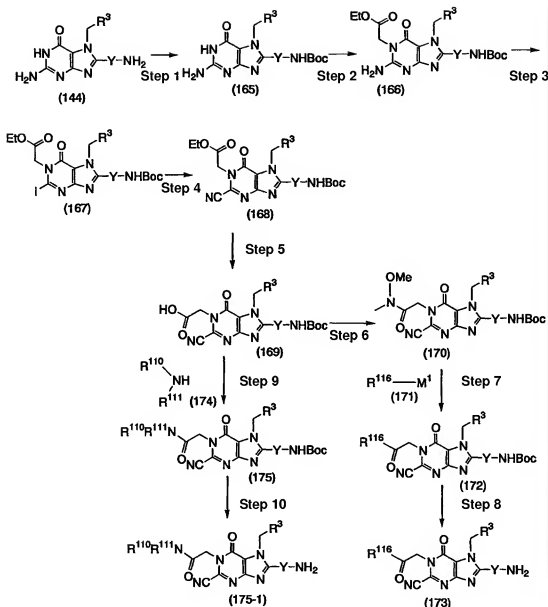
Compound (163) can be produced from compound (162) in the same manner as noted in the literature (such as Tetrahedron Lett. 39, 6667 (1998) and J. Am. Chem. Soc. 100, 5437 (1978)).

7) Step 7

Compound (164) can be produced from compound (163) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 27

Compounds, and their salts, represented by Formulas (173) and (175-1) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^3 and Y are defined the same as in section [1], M^1 is the same as in Manufacturing Method 22, $R^{116}C(O)$ is the same as in Manufacturing Method 23, and $R^{110}R^{111}NC(O)$ is the same as in Manufacturing Method 25.)

1) Step 1

Compound (165) can be produced from compound (144) in the same manner as in Step 1 of Manufacturing Method 10.

2) Step 2

Compound (166) can be produced from compound (165) in the same manner as in

Step 6 of Manufacturing Method 13.

3) Step 3

Compound (167) can be produced from compound (166) in the same manner as in Step 2 of Manufacturing Method 26.

4) Step 4

Compound (168) can be produced from compound (167) in the same manner as in Step 3 of Manufacturing Method 26.

5) Step 5

Compound (169) can be produced from compound (168) in the same manner as in Step 4 of Manufacturing Method 19.

6) Steps 6 and 7

Compound (172) can be produced from compound (169) in the same manner as in Steps 2 and 3 of Manufacturing Method 23. Compound (171) can be a commercially available product or produced in the same manner as noted in Course in Experimental Chemistry (Ed. Chemical Society of Japan, Maruzen), Vol. 25.

7) Step 8

Compound (173) can be produced from compound (172) in the same manner as in Step 2 of Manufacturing Method 2.

8) Step 9

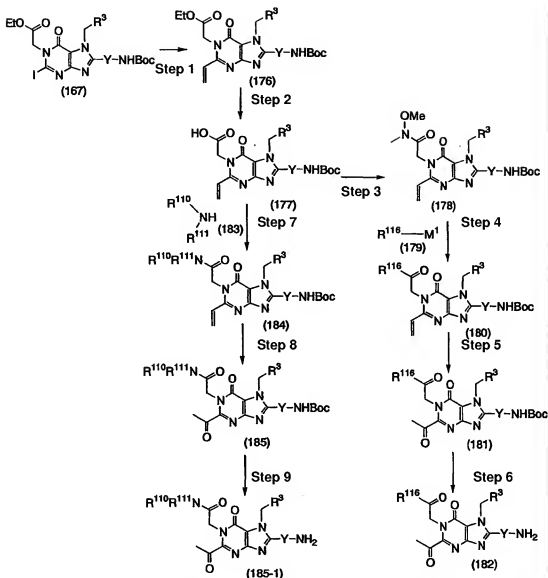
Compound (175) can be produced from compound (169) in the same manner as in Step 5 of Manufacturing Method 19.

9) Step 10

Compound (175-1) can be produced from compound (175) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 28

Compounds, and their salts, represented by Formulas (182) and (185-1) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R³ and Y are defined the same as in section [1], M¹ is the same as in Manufacturing Method 22, R¹¹⁶C(O) is the same as in Manufacturing Method 23, and R¹¹⁰R¹¹¹NC(O) is the same as in Manufacturing Method 25.)

1) Step 1

Compound (176) can be produced from compound (167) in the same manner as in Step 5 of Manufacturing Method 26.

2) Step 2

Compound (177) can be produced from compound (176) in the same manner as in

Step 4 of Manufacturing Method 19.

3) Steps 3 and 4

Compound (180) can be produced from compound (177) in the same manner as in Steps 2 and 3 of Manufacturing Method 23. Compound (179) can be a commercially available product or produced in the same manner as noted in Course in Experimental Chemistry (Ed. Chemical Society of Japan, Maruzen), Vol. 25.

4) Step 5

Compound (181) can be produced from compound (180) in the same manner as in Step 6 of Manufacturing Method 26.

5) Step 6

Compound (182) can be produced from compound (181) in the same manner as in Step 2 of Manufacturing Method 2.

6) Step 7

Compound (184) can be produced from compound (177) in the same manner as in Step 5 of Manufacturing Method 19.

7) Step 8

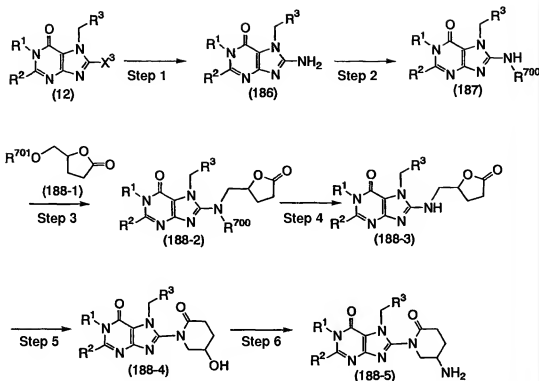
Compound (185) can be produced from compound (184) in the same manner as in Step 6 of Manufacturing Method 26.

8) Step 9

Compound (185-1) can be produced from compound (185) in the same manner as in Step 2 of Manufacturing Method 2.

Manufacturing Method 29

Compounds, and their salts, represented by Formula (188-5) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^2 , and R^3 are the same as in section [1], X^3 is the same as in Manufacturing Method 1, R^{700} is a p-nitrobenzenesulfonyl group or o-nitrobenzenesulfonyl group, and R^{701} is a hydrogen atom, benzenesulfonyl group, p-toluenesulfonyl group, or methanesulfonyl group.)

1) Step 1

Compound (186) can be produced from compound (12) in the same manner as noted in the literature (such as *Heterocycles* 38, 529 (1994)).

2) Step 2

Compound (187) can be produced from compound (186) in the same manner as noted in the literature (such as *Tetrahedron Lett.* 42, 871 (2001)).

3) Step 3

When R^{701} is a hydrogen atom, compound (188-2) can be produced from compound (187) in the same manner noted in the literature (such as *Tetrahedron Lett.* 42, 871 (2001)). When R^{701} is a benzenesulfonyl group, p-toluenesulfonyl group, or methanesulfonyl group, compound (188-2) can be produced from (compound 187) in the same manner noted in the literature (such as *Comprehensive Organic transformation*,

R.C. Larock, VCH publisher Inc., (1989)). Compound (188-1) includes optically active isomers.

4) Steps 4 and 5

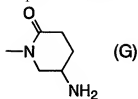
Compound (188-4) can be produced from compound (188-2) in the same manner noted in the literature (such as Tetrahedron Lett. 42, 871 (2001)).

5) Step 6

Compound (188-5) can be produced from compound (188-4) in the same manner as in Steps 2 to 4 of Manufacturing Method 10.

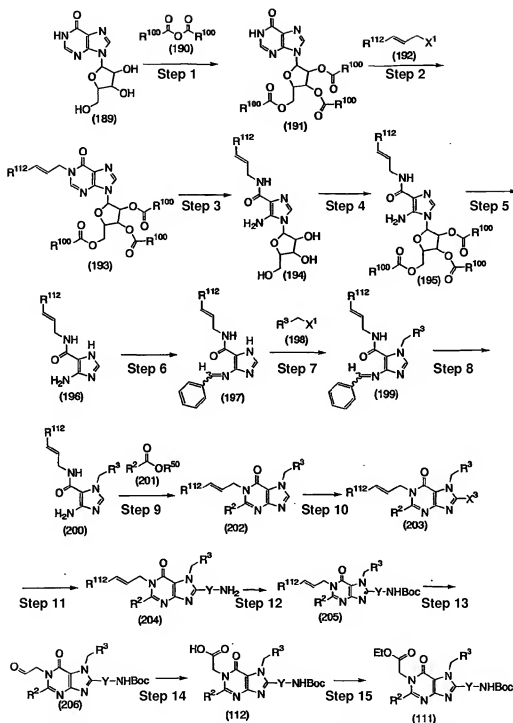
Manufacturing Method 30

Compound (57) of Manufacturing Method 13, Compound (56-5) of Manufacturing Method 13, Compound (84) of Manufacturing Method 17, Compound (134) of Manufacturing Method 21, Compound (204) of Manufacturing Method 31, and Compound (144) of Manufacturing Method 25, wherein Y-NH₂ is represented by Formula (G) below, can be produced from the corresponding starting materials Compound (56-2) of Manufacturing Method 13, Compound (56-4) of Manufacturing Method 13, Compound (83) of Manufacturing Method 17, Compound (133) of Manufacturing Method 21, Compound (203) of Manufacturing Method 31, and Compound (56) of Manufacturing Method 25, respectively, in the same manner as in Steps 1 to 6 of Manufacturing Method 29.



Manufacturing Method 31

Compound (111) of Manufacturing Method 19 can be produced in the following manner, for example.



(Where R^2 , R^3 , and Y are defined the same as in section [1], R^{100} , X^1 and X^3 are the same as in Manufacturing Method 1, R^{50} is the same as in Manufacturing Method 11, and R^{112} is methyl, ethyl, propyl, 2-propyl, or phenyl.)

1) Step 1

Compound (191) can be produced from compound (189) in the same manner as in Step 1 of Manufacturing Method 1.

2) Step 2

Compound (193) can be produced from compound (191) in the same manner as in Step 6 of Manufacturing Method 1.

3) Step 3

Compound (194) can be produced from compound (193) in the same manner as in Step 2 of Manufacturing Method 18.

4) Step 4

Compound (195) can be produced from compound (194) in the same manner as in Step 1 of Manufacturing Method 1.

5) Step 5

Compound (196) can be produced from compound (195) in the same manner as in Step 5 of Manufacturing Method 1.

6) Steps 6 to 8

Compound (200) can be produced from compound (196) in the same manner as in Steps 1 to 3 of Manufacturing Method 21.

7) Step 9

Compound (202) can be produced from compound (200) in the same manner as in Step 1 of Manufacturing Method 11.

8) Step 10

Compound (203) can be produced from compound (202) in the same manner as in Step 3 of Manufacturing Method 11. An example of a preferred base in this step is tert-butyl lithium.

9) Step 11

Compound (204) can be produced from compound (203) in the same manner as in Steps 8 to 11 of Manufacturing Method 1.

10) Step 12

Compound (205) can be produced from compound (204) in the same manner as in

Step 1 of Manufacturing Method 10.

11) Step 13

Compound (206) can be produced from compound (205) in the same manner as in Step 1 of Manufacturing Method 22.

12) Step 14

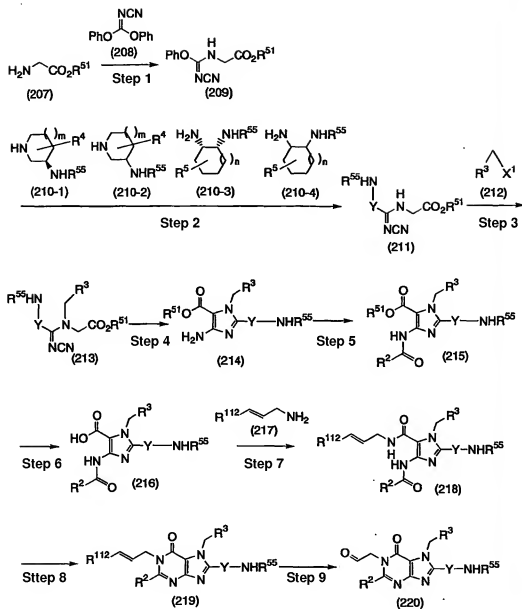
Compound (112) can be produced from compound (206) in the same manner noted in the literature (such as Tetrahedron Letters 37, 2573 (1996), Tetrahedron 52, 8989 (1996), Synlett 1555 (2001), and Synlett 1599 (2001)).

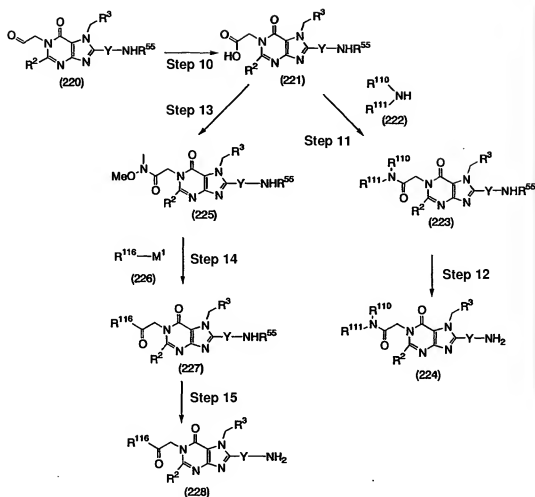
13) Step 15

Compound (111) can be produced from compound (112) by the same methods as noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

Manufacturing Method 32

Compounds, and their salts, represented by Formulas (224) and (228) out of the compounds represented by Formula (I) can be produced in the following manner, for example.





(Where m, n, R^2, R^3, R^4, R^5 , and Y are defined the same as in section [1], M^1 is the same as in Manufacturing Method 22, R^{51} is methyl, ethyl, 3-methyl-2-butenyl, or 2-propenyl, R^{55} is Boc or Cbz, R^{112} is the same as in Manufacturing Method 31, $R^{116}C(O)$ is the same as in Manufacturing Method 23, and $R^{110}R^{111}NC(O)$ is the same as in Manufacturing Method 25.)

1) Step 1

Compound (209) can be produced from compound (207) in the same manner as noted in the literature (such as Bioorg. Med. Chem. Lett. 12, 653 (2002), Chem. Pharm. Bull. 45, 2005 (1997), Tetrahedron Letters 39, 7983 (1998), Tetrahedron 46, 7803 (1990), Tetrahedron Letters 32, 691 (1991), Tetrahedron 51, 5369 (1995), J. Med. Chem. 38, 3236 (1995), and J. Heterocycl. Chem. 24, 275 (1987)).

2) Step 2

Compound (211) can be produced from compound (209) in the same manner as in Step 8 or 9 of Manufacturing Method 1.

3) Step 3

Compound (213) can be produced from compound (211) in the same manner as in Step 6 of Manufacturing Method 1.

4) Step 4

Compound (214) can be produced from compound (213) in the same manner as noted in the literature (such as WO 02/068420).

5) Step 5

Compound (215) can be produced from compound (214) in the same manner as noted in the literature (such as WO 99/03858, Tetrahedron Letters 38, 7963 (1997), Bioorg. Med. Chem. Lett. 12, 543 (2002), Heterocycles 57, 123 (2002), Tetrahedron Letters 41, 9957 (2000), and Tetrahedron Letters 42, 2201 (2001)).

6) Step 6

When R⁵¹ is a methyl group or ethyl group, compound (216) can be produced from compound (215) in the same manner as in Step 4 of Manufacturing Method 19 or as noted in the literature (such as WO 99/64426). When R⁵¹ is a 3-methyl-2-butenyl group, compound (216) can be produced from compound (215) in the same manner as noted in the literature (such as Synlett 137 (2002)). When R⁵¹ is a 2-propenyl group, compound (216) can be produced from compound (215) in the same manner as noted in the literature (such as Synlett 722 (2000), Tetrahedron 57, 3435 (2001), Tetrahedron 56, 5353 (2000), J. Org. Chem. 67, 4975 (2002), and J. Org. Chem. 63, 9103 (1998).

7) Step 7

Compound (218) can be produced from compound (216) in the same manner as noted in the literature (such as Bioorg. Med. Chem. Lett. 6, 1483 (1996), Tetrahedron Letters

37, 7031 (1996), Tetrahedron Letters 37, 8081 (1996), Tetrahedron Letters 41, 6171 (2000), and Synth. Commun. 23, 2265 (1993)).

8) Step 8

Compound (219) can be produced from compound (218) in the same manner as noted in the literature (such as WO 99/03858).

9) Step 9

Compound (220) can be produced from compound (219) in the same manner as in Step 1 of Manufacturing Method 22.

10) Step 10

Compound (221) can be produced from compound (220) in the same manner as in Step 14 of Manufacturing Method 31.

11) Step 11

Compound (223) can be produced from compound (221) in the same manner as in Step 5 of Manufacturing Method 19.

12) Step 12

When R^{55} is Boc, compound (224) can be produced from compound (223) in the same manner as in Step 2 of Manufacturing Method 2. When R^{55} is Cbz, compound (224) can be produced from compound (223) in the same manner as noted in the literature (such as J. Am. Chem. Soc. 85, 2149 (1963), Tetrahedron Lett. 41, 3029 (2000), and Tetrahedron Lett. 36, 8677 (1995)). When compound (224) is a racemate, optically active forms can be produced in the same manner as in Step 10 of Manufacturing Method 1.

13) Steps 13 and 14

Compound (227) can be produced from compound (221) in the same manner as in Steps 2 and 3 of Manufacturing Method 23. Compound (226) can be a commercially available product or produced, for example, by the method noted in Course in Experimental Chemistry (Ed. Chemical Society of Japan, Maruzen), Vol. 25.

14) Step 15

When R^{55} is Boc, compound (228) can be produced from compound (227) in the same manner as in Step 2 of Manufacturing Method 2. When R^{55} is Cbz, compound (228)

can be produced from compound (227) in the same manner as noted in the literature (such as J. Am. Chem. Soc. 85, 2149 (1963), Tetrahedron Lett. 41, 3029 (2000), and Tetrahedron Lett. 36, 8677 (1995)). When compound (228) is a racemate, optically active forms can be produced in the same manner as in Step 10 of Manufacturing Method 1.

Manufacturing Method 33

Compound (210-1) of Manufacturing Method 32 can be produced in the following manner.



(Where m and R⁴ are defined the same as in section [1], and R⁵⁵ is the same as in Manufacturing Method 32.)

1) Step 1

Compound (210-1) can be produced from compound (21) in the same manner as noted in the literature (such as J. Chem. Soc., Perkin Trans. 1, 2233 (1999)).

Manufacturing Method 34

Compound (210-2) of Manufacturing Method 32 can be produced in the following manner.



(Where m and R⁴ are defined the same as in section [1], and R⁵⁵ is the same as in Manufacturing Method 32.)

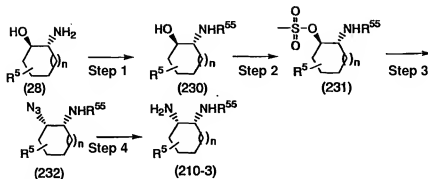
1) Step 1

Compound (210-2) can be produced from compound (13) in the same manner as in

Step 1 of Manufacturing Method 33.

Manufacturing Method 35

Compound (210-3) of Manufacturing Method 32 can be produced in the following manner.



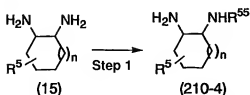
(Where n and R⁵ are defined the same as in section [1], and R⁵⁵ is the same as in Manufacturing Method 32.)

1) Steps 1 to 4

Compound (210-3) can be produced from compound (28) in the same manner as in Steps 1 to 4 of Manufacturing Method 10.

Manufacturing Method 36

Compound (210-4) of Manufacturing Method 32 can be produced in the following manner.



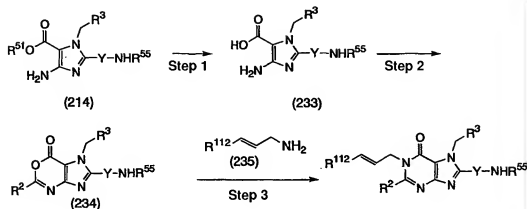
(Where n and R⁵ are defined the same as in section [1], and R⁵⁵ is the same as in Manufacturing Method 32.)

1) Step 1

Compound (210-4) can be produced from compound (15) in the same manner as in Step 1 of Manufacturing Method 33.

Manufacturing Method 37

Compound (219) of Manufacturing Method 32 can be produced in the following manner.



(Where R², R³, and Y are defined the same as in section [1], R⁵¹ and R⁵⁵ are the same as in Manufacturing Method 32, and R¹¹² is the same as in Manufacturing Method 31.)

1) Step 1

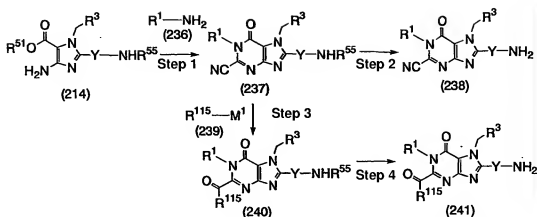
Compound (233) can be produced from compound (214) in the same manner as in Step 4 of Manufacturing Method 19.

2) Steps 2 and 3

Compound (219) can be produced from compound (233) in the same manner as noted in the literature (such as J. Med. Chem. 15, 106 (1972)).

Manufacturing Method 38

Compounds (238) and (241) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], $R^{115}C(O)$ is the same as in Manufacturing Method 22, R^{51} and R^{55} are the same as in Manufacturing Method 32, and M^1 is the same as in Manufacturing Method 22.)

1) Step 1

Compound (237) can be produced from compounds (214) and (236) in the same manner as noted in the literature (such as J. Heterocycl. Chem. 35, 659 (1998)).

2) Step 2

Compound (238) can be produced from compound (237) in the same manner as in Step 12 of Manufacturing Method 32.

3) Step 3

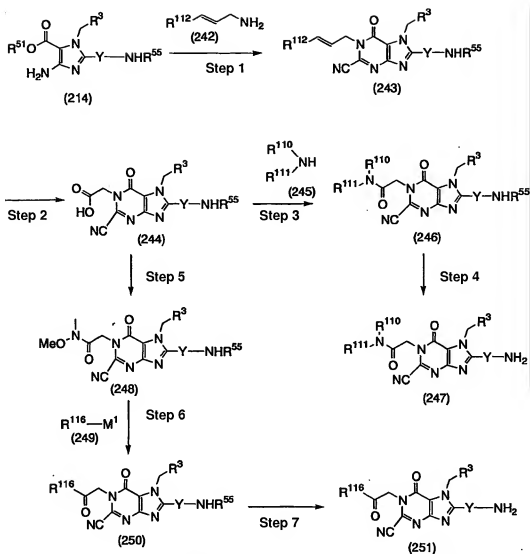
Compound (240) can be produced from compound (237) in the same manner as noted in the literature (such as J. Org. Chem. 59, 4844 (1994)).

4) Step 4

Compound (241) can be produced from compound (240) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 39

Compounds (247) and (251) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^3 , and Y are defined the same as in section [1], M^1 is the same as in Manufacturing Method 22, R^{51} and R^{55} are the same as in Manufacturing Method 32, R^{112} is the same as in Manufacturing Method 31, and $R^{116}C(O)$ is the same as in Manufacturing Method 25.)

1) Step 1

Compound (243) can be produced from compounds (214) and (242) in the same manner as in Step 1 of Manufacturing Method 38.

2) Step 2

Compound (244) can be produced from compound (243) in the same manner as in Step 1 of Manufacturing Method 22 and Step 14 of Manufacturing Method 31.

3) Step 3

Compound (246) can be produced from compound (244) in the same manner as in Step 5 of Manufacturing Method 19.

4) Step 4

Compound (247) can be produced from compound (246) in the same manner as in Step 12 of Manufacturing Method 32.

5) Steps 5 and 6

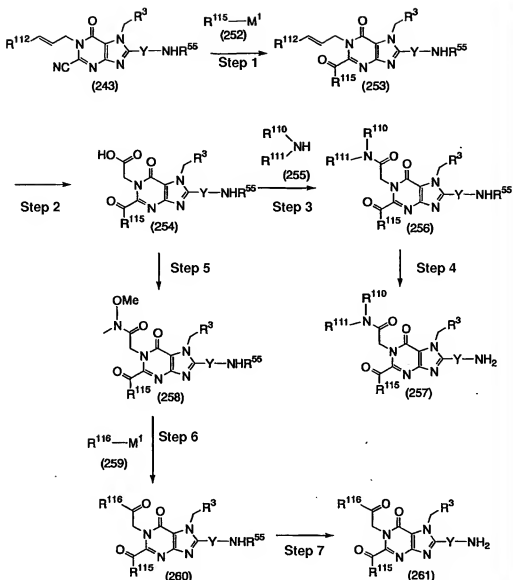
Compound (250) can be produced from compound (244) in the same manner as in Steps 2 and 3 of Manufacturing Method 23.

6) Step 7

Compound (251) can be produced from compound (250) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 40

Compounds (257) and (261) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^3 , and Y are defined the same as in section [1], M^1 is the same as in Manufacturing Method 22, R^{55} is the same as in Manufacturing Method 32, R^{112} is the same as in Manufacturing Method 31, $R^{116}C(O)$ is the same as in Manufacturing Method 23, $R^{115}C(O)$ is the same as in Manufacturing Method 22, and $R^{110}R^{111}NC(O)$ is the same as in Manufacturing Method 25.)

1) Step 1

Compound (253) can be produced from compound (243) in the same manner as in Step 3 of Manufacturing Method 38.

2) Step 2

Compound (254) can be produced from compound (253) in the same manner as in Step 1 of Manufacturing Method 22 and Step 14 of Manufacturing Method 31.

3) Step 3

Compound (256) can be produced from compound (254) in the same manner as in Step 5 of Manufacturing Method 19.

4) Step 4

Compound (257) can be produced from compound (256) in the same manner as in Step 12 of Manufacturing Method 32.

5) Steps 5 and 6

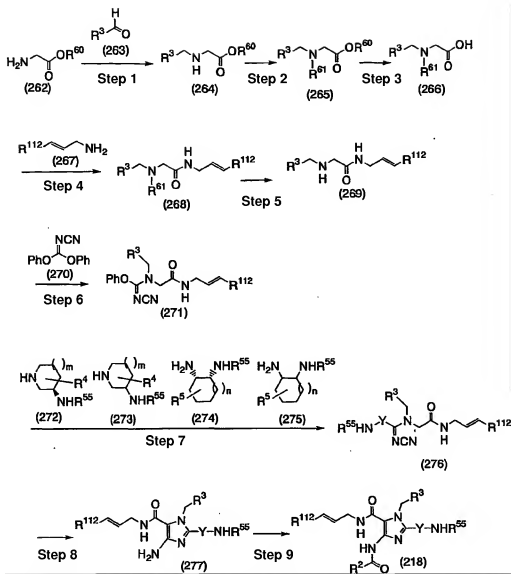
Compound (260) can be produced from compound (254) in the same manner as in Steps 2 and 3 of Manufacturing Method 23.

6) Step 7

Compound (261) can be produced from compound (260) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 41

Compound (218) of Manufacturing Method 32 can be produced in the following manner, for example.



(Where m , n , R^2 , R^3 , R^4 , R^5 , and Y are defined the same as in section [1], R^{112} is the same as in Manufacturing Method 31, R^{55} is the same as in Manufacturing Method 32, R^{60} is methyl or ethyl, and R^{61} is Boc.)

1) Step 1

Compound (264) can be produced from compound (262) in the same manner as noted in the literature (such as WO 00/18790).

2) Step 2

Compound (265) can be produced from compound (264) in the same manner as in

Step 3 of Manufacturing Method 9.

3) Step 3

Compound (266) can be produced from compound (265) in the same manner as in Step 4 of Manufacturing Method 19.

4) Step 4

Compound (268) can be produced from compound (266) in the same manner as in Step 5 of Manufacturing Method 19.

5) Step 5

Compound (269) can be produced from compound (268) in the same manner as in Step 2 of Manufacturing Method 2.

6) Step 6

Compound (271) can be produced from compound (269) in the same manner as in Step 1 of Manufacturing Method 32.

7) Step 7

Compound (276) can be produced from compound (271) in the same manner as in Steps 8 and 9 of Manufacturing Method 1.

8) Step 8

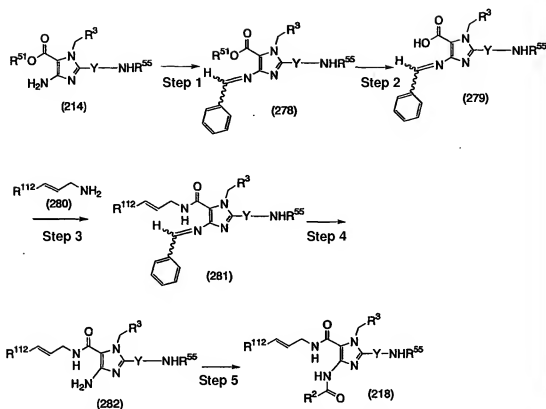
Compound (277) can be produced from compound (276) in the same manner as in Step 4 of Manufacturing Method 32.

9) Step 9

Compound (218) can be produced from compound (277) in the same manner as in Step 5 of Manufacturing Method 32.

Manufacturing Method 42

Compound (218) of Manufacturing Method 32 can be produced in the following manner, for example.



(Where R^2 , R^3 , and Y are defined the same as in section [1], R^{51} and R^{55} are the same as in Manufacturing Method 32, and R^{112} is the same as in Manufacturing Method 31.)

1) Step 1

Compound (278) can be produced from compound (214) in the same manner as in Step 1 of Manufacturing Method 21.

2) Step 2

Compound (279) can be produced from compound (278) in the same manner as in Step 6 of Manufacturing Method 32.

3) Step 3

Compound (281) can be produced from compound (279) in the same manner as in Step 7 of Manufacturing Method 32.

4) Step 4

Compound (282) can be produced from compound (281) in the same manner as in Step 3 of Manufacturing Method 21. When R^{55} of compound (281) is Boc, compounds in

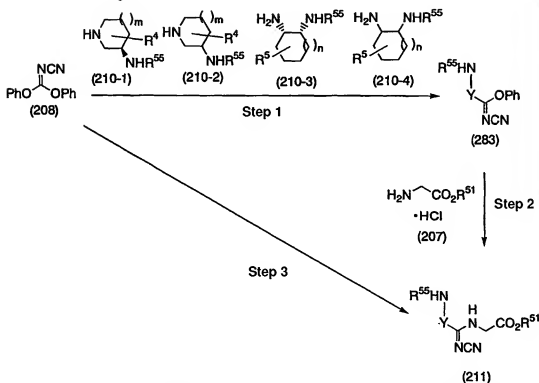
which R^{55} of compound (282) is a hydrogen atom may be produced, but R^{55} of compound (282) can be changed from a hydrogen atom to Boc in the same manner as in Step 1 of Manufacturing Method 10.

5) Step 5

Compound (218) can be produced from compound (282) in the same manner as in Step 5 of Manufacturing Method 32.

Manufacturing Method 43

Compound (211) of Manufacturing Method 32 can be produced in the following manner, for example.



(Where m , n , R^4 , R^5 , and Y are defined the same as in section [1], and R^{51} and R^{55} are the same as in Manufacturing Method 32.)

1) Step 1

Compound (283) can be produced from compound (208) in the same manner as in Step 2 of Manufacturing Method 32.

2) Step 2

Compound (211) can be produced from compound (283) in the same manner as in Step 1 of Manufacturing Method 32.

3) Step 3

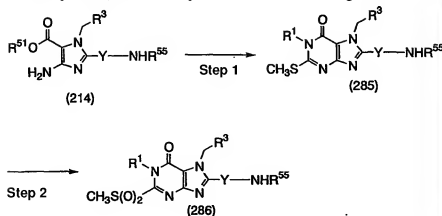
Compound (211) can be produced from compound (208) by the reactions shown in (1) and (2) below.

(1) Compound (208) is allowed to react with compounds (210-1), (210-2), (210-3), or (210-4) in an inert solvent. Examples of inert solvents include alcohol-based solvents such as methanol, ethanol, and 2-propanol.

(2) A reaction is carried out with the addition of a base and compound (207) to the reaction mixture of (1) in Step 3 of Manufacturing Method 43. Examples of bases include organic bases such as imidazole, triethylamine, diisopropylethylamine, tributylamine, 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undeca-7-ene, 4-(dimethylamino)pyridine, or picoline, and preferably triethylamine. The amount of compound (207) may normally be selected from the range of 3 to 10 equivalents relative to compound (208). The amount of the base may normally be selected from the range of 5 to 15 equivalents relative to compound (208). The reaction temperature may be selected from the range of about 50 to about 150°C.

Manufacturing Method 44

Compound (286) can be produced in the following manner, for example.

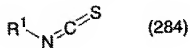


(Where R^1 , R^3 , and Y are defined the same as in section [1], and R^{51} and R^{55} are the same as in Manufacturing Method 32.)

1) Step 1

Compound (285) can be produced from compound (214) by the reactions shown in (1) through (3) below.

Compound (214) is allowed to react with compound (284) represented by the following formula in the presence of a base in pyridine.



(Where R^1 is the same as in section [1].) The reaction temperature can be selected from the range of about 50 to about 150°C. The amount of compound (284) may normally be selected from the range of 1 to 3 equivalents.

(2) A reaction is brought about with the addition of a base to the reaction mixture of (1) Step 1 in Manufacturing Method 44. Examples of bases include cesium carbonate, potassium carbonate, and sodium carbonate. The amount of the base may normally be selected from the range of 1 to 5 equivalents. The reaction temperature may be selected from the range of about 50 to about 150°C.

(3) A reaction is brought about with the addition of methyl iodide to the reaction mixture of (2) Step 1 in Manufacturing Method 44. The amount of the methyl iodide may normally be selected from the range of 1 to 5 equivalents. The reaction temperature may be selected from the range of about -10 to about 40°C.

2) Step 2

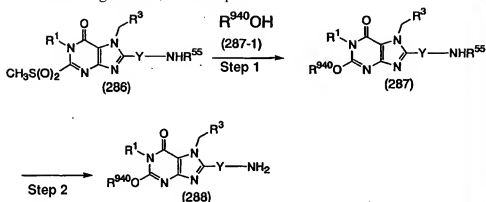
The following manufacturing methods (A) and (B) can be used as Step 2.

Manufacturing Method (A): Compound (286) can be produced by allowing compound (285) to react with a mixture of sodium tungstate and hydrogen peroxide aqueous solution in an inert solvent. Examples of inert solvents include alcohol based-solvents (such as ethanol, methanol, and 2-propanol) or organic acids (such as acetic acid or propionic acid). A mixture of alcohol and organic acid is usually used. The amount of sodium tungstate may normally be selected from the range of 1 to 5 equivalents relative to compound (285). The amount of hydrogen peroxide aqueous solution (usually 30% aqueous solution) may normally be selected from the range of 10 to 100 equivalents relative to compound (285). The reaction temperature may be selected from the range of about -10 to about 40°C.

Manufacturing Method (B): Compound (286) can be produced by allowing compound (285) to react with Oxone (registered trademark, by Aldrich) in an inert solvent. Examples of inert solvents include alcohol based-solvents (such as ethanol, methanol, and 2-propanol). The amount of Oxone (registered trademark, by Aldrich) may normally be selected from the range of 1 to 20 equivalents relative to compound (285). The reaction temperature may be selected from the range of about -10 to about 40°C.

Manufacturing Method 45

Compound (288) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], R^{51} is the same as in Manufacturing Method 32, and $R^{94}O$ represents the “optionally substituted alkoxy groups,” “optionally substituted aryloxy groups,” “optionally substituted aralkyloxy groups,” or “optionally substituted heteroaryloxy groups” of R^2 in section [1] or groups represented by (T1) through (T6).)

1) Step 1

Compound (287) can be produced by bringing about a reaction with compound (287-1) which has reacted with a base and compound (286) in an inert solvent. Examples of bases include potassium tert-butoxide, sodium tert-butoxide, cesium carbonate, potassium carbonate, sodium phenoxide, potassium phenoxide, and sodium hydride, and preferably sodium hydride. The amount of the base may normally be selected from the range of 1 to 5 equivalents relative to compound (287-1). Examples of

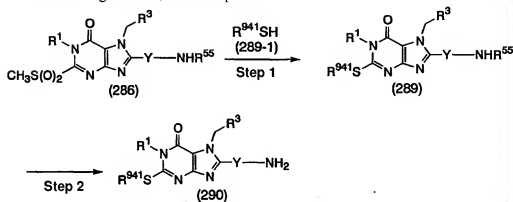
inert solvents include tetrahydrofuran, 1,4-dioxane, N,N-dimethyl formamide, or mixtures of such solvents. The reaction temperature may be selected from the range of about -10 to about 50°C.

2) Step 2

Compound (288) can be produced from compound (287) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 46

Compound (290) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], R^{55} is the same as in Manufacturing Method 32, and $R^{941}S$ represents the “optionally substituted alkylthio groups” or “optionally substituted arylthio groups” of R^2 in section [1].)

1) Step 1

Compound (289) can be produced from compound (286) in the same manner as in Step 1 of Manufacturing Method 45.

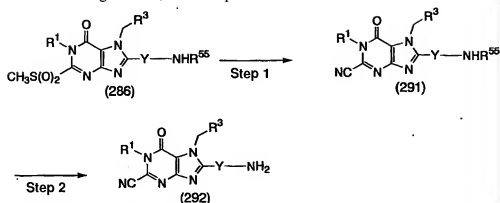
2) Step 2

Compound (290) can be produced from compound (289) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 47

Compound (292) out of the compounds represented by Formula (I) can be produced

in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], and R^{55} is the same as in Manufacturing Method 32.)

1) Step 1

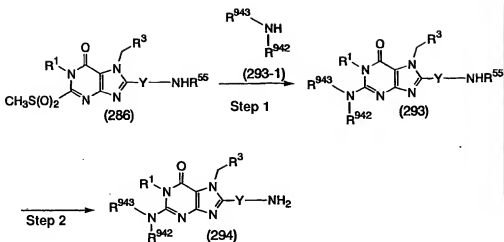
Compound (291) can be produced by a reaction between compound (286) and sodium cyanide or potassium cyanide in an inert solvent. The amount of the sodium cyanide or potassium cyanide may normally be selected from the range of 0.8 to 5 equivalents relative to compound (286). Examples of inert solvents include tetrahydrofuran, 1,4-dioxane, N,N-dimethyl formamide, or mixtures of such solvents. The reaction temperature may be selected from the range of about -10 to about 50°C .

2) Step 2

Compound (290) can be produced from compound (289) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 48

Compound (294) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], R^{55} is the same as in Manufacturing Method 32, and $\text{R}^{942}\text{R}^{943}\text{N}$ represents the “optionally substituted nitrogen-bearing saturated heterocyclic groups” and “optionally substituted amino groups” of R^2 in section [1].)

1) Step 1

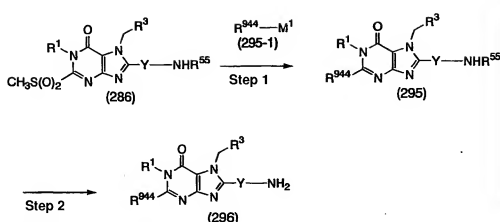
Compound (293) can be produced by a reaction between compound (286) and compound (293-1) in the presence or absence of an inert solvent. The amount of compound (293-1) may normally be selected from the range of 10 to 100 equivalents relative to compound (286). Compound (293-1) can be used as solvent when in the form of a liquid. Examples of inert solvents include alcohol based-solvents (such as ethanol, methanol, and 2-propanol). The reaction temperature may be selected from the range of about 50 to about 150°C.

2) Step 2

Compound (294) can be produced from compound (293) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 49

Compound (296) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R¹, R³, and Y are defined the same as in section [1], M¹ is the same as in Manufacturing Method 22, R⁵⁵ is the same as in Manufacturing Method 32, and R⁹⁴² represents the "optionally substituted alkyl groups," "optionally substituted cycloalkyl groups," "optionally substituted alkenyl groups," or "optionally substituted aryl groups," "optionally substituted heteroaryl groups," "optionally substituted heteroarylalkyl," and "optionally substituted aralkyl groups" of R² in section [1].

1) Step 1

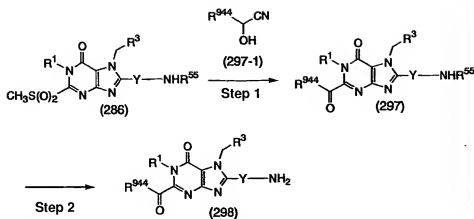
Compound (295) can be produced by a reaction between compound (286) and compound (295-1) in an inert solvent. The amount of compound (295-1) may normally be selected from the range of 3 to 10 equivalents relative to compound (286). Examples of inert solvents include tetrahydrofuran, 1,4-dioxane, N,N-dimethyl formamide, or mixtures of such solvents. The reaction temperature may be selected from the range of about -10 to about 50°C.

2) Step 2

Compound (296) can be produced from compound (295) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 50

Compound (298) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], R^{55} is the same as in Manufacturing Method 32, and $\text{R}^{944}\text{C(O)}$ represents the "optionally substituted aroyl groups" and "optionally substituted nitrogen-bearing heteroarylcarbonyl groups" of R^2 in section [1].)

1) Step 1

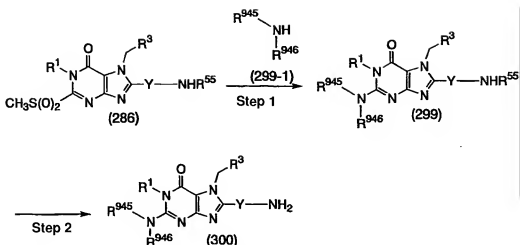
Compound (297) can be produced by a reaction between compound (286) and compound (297-1) in an inert solvent in the presence of a base. The amount of compound (297-1) may normally be selected from the range of 3 to 10 equivalents relative to compound (286). Examples of bases include sodium hydride. Examples of inert solvents include tetrahydrofuran, 1,4-dioxane, *N,N*-dimethyl formamide, or mixtures of such solvents. The reaction temperature may be selected from the range of about 50 to about 150°C.

2) Step 2

Compound (298) can be produced from compound (297) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 51

Compound (300) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



(Where R^1 , R^3 , and Y are defined the same as in section [1], R^{55} is the same as in Manufacturing Method 32, and $R^{945}R^{946}N$ represents the “optionally substituted heteroaryl groups (such as pyrrole, imidazole, and pyrazole)” and “optionally substituted amino groups” of R^2 in section [1].)

1) Step 1

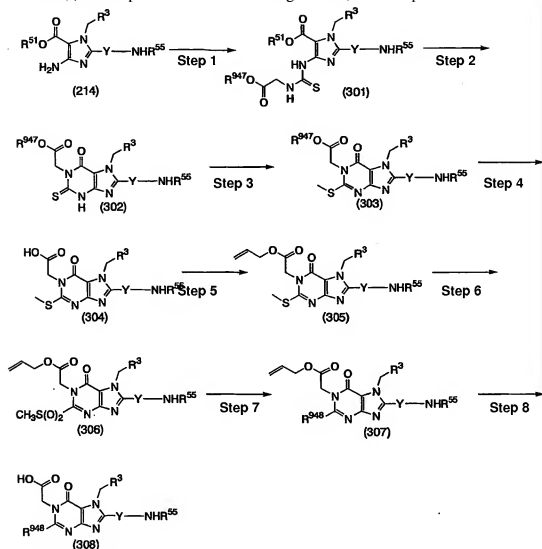
Compound (299) can be produced by allowing compound (299-1) to react with compound (286) and a base in an inert solvent. Examples of bases include potassium tert-butoxide, sodium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, sodium phenoxide, potassium phenoxide, and sodium hydride, and preferably sodium hydride. The amount of the base may normally be selected from the range of 1 to 3 equivalents relative to compound (299-1). The amount of compound (299-1) may normally be selected from the range of 2 to 10 equivalents relative to compound (286). Examples of inert solvents include tetrahydrofuran, 1,4-dioxane, N,N-dimethyl formamide, or mixtures of such solvents. The reaction temperature may be selected from the range of about -10 to about 50°C .

2) Step 2

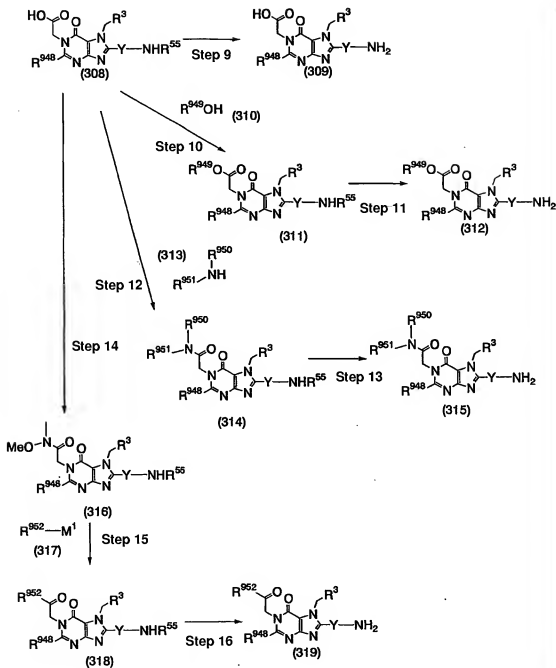
Compound (300) can be produced from compound (299) in the same manner as in Step 12 of Manufacturing Method 32.

Manufacturing Method 52

Compounds (309), (312), (315), and (319) out of the compounds represented by Formula (I) can be produced in the following manner, for example.



202



(Where R^3 and Y are defined the same as in section [I], M^1 is the same as in Manufacturing Method 22, R^{51} and R^{55} are the same as in Manufacturing Method 32, R^{947} is methyl, ethyl, propyl, or 2-propyl, $R^{949}OC(O)$ represents the "optionally substituted alkoxy carbonyl groups" given as examples of substituents for the "optionally substituted alkyl groups" of R^1 and R^2 in section [I], $R^{950}R^{951}NC(O)$ represents the "optionally

substituted carbamoyl groups" given as examples of substituents for the "optionally substituted alkyl groups" of R^1 and R^2 in section [I], $R^{952}C(O)$ represents the "optionally substituted aroyl groups" given as examples of substituents for the "optionally substituted alkyl groups" of R^1 and R^2 in section [I], and R^{948} represents the "optionally substituted alkoxy groups," "optionally substituted aryloxy groups," optionally substituted aralkyloxy groups," "optionally substituted heteroaryloxy groups," "optionally substituted alkylthio groups," "optionally substituted arylthio groups," "optionally substituted alkyl groups," "optionally substituted cycloalkyl groups," "optionally substituted alkenyl substituents," "optionally substituted aryl groups," "optionally substituted heteroaryl groups," "optionally substituted heteroarylalkyls," and "optionally substituted aralkyl groups," "optionally substituted amino groups," "optionally substituted nitrogen-bearing saturated heterocyclic groups," "optionally substituted heteroaryl groups (such as pyrrole, imidazole, and pyrazole)," "optionally substituted aroyl groups," and "optionally substituted nitrogen-bearing heteroarylcarbonyl groups" of R^2 in section [I].)

Steps 1 to 3

Compound (303) can be produced from compound (214) in the same manner as noted in the literature (such as J. Heterocyclic Chem. 36, 1119 (1999)).

Step 4

Compound (304) can be produced from compound (303) in the same manner as in Step 6 of Manufacturing Method 32.

Step 5

Compound (305) can be produced from compound (304) in the same manner as noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

4) Step 6

Compound (306) can be produced from compound (305) in the same manner as in Step 2 of Manufacturing Method 44.

Step 7

Compound (307) can be produced from compound (306) in the same manner as in Step 1 of Manufacturing Method 45, Step 1 of Manufacturing Method 46, Step 1 of Manufacturing Method 47, Step 1 of Manufacturing Method 48, Step 1 of Manufacturing Method 49, Step 1 of Manufacturing Method 50, and Step 1 of Manufacturing Method 51. Step 8

Compound (308) can be produced from compound (307) in the same manner as in Step 6 of Manufacturing Method 32.

7) Step 9

Compound (309) can be produced from compound (308) in the same manner as in Step 15 of Manufacturing Method 32.

8) Step 10

Compound (311) can be produced from compound (308) in the same manner as noted in the literature (such as Comprehensive Organic transformation, R.C. Larock, VCH publisher Inc., (1989)).

9) Step 11

Compound (312) can be produced from compound (311) in the same manner as in Step 15 of Manufacturing Method 32.

10) Step 12

Compound (314) can be produced from compound (308) in the same manner as in Step 5 of Manufacturing Method 19.

11) Step 13

Compound (315) can be produced from compound (314) in the same manner as in Step 15 of Manufacturing Method 32.

12) Steps 14 and 15

Compound (318) can be produced from compound (308) in the same manner as in Steps 2 and 3 of Manufacturing Method 23.

13) Step 16

Compound (319) can be produced from compound (318) in the same manner as in Step 15 of Manufacturing Method 32.

The starting material compounds in the steps of the above manufacturing methods can also be used in the form of salts. In addition, when the starting material compounds of the reactions have groups that will be active in the reaction, such as hydroxyl groups, amino groups, and carboxyl groups, those groups can be protected in advance as needed with suitable protective groups at sites other than sites intended for reaction, and the protective groups can be eliminated after the various reactions or after a few reactions, giving the target product. Any protective group commonly used in the field of organic synthetic chemistry may be used as protective groups to protect hydroxyl groups, amino groups, carboxyl groups, or the like, and such protective groups can be introduced and removed according to common methods (such as the methods described in *Protective Groups in Organic Synthesis*, T.W. Greene and P.G.M. Wuts, 2nd Edition, John Wiley & Sons, Inc. (1991)).

Examples of protective groups for a hydroxyl group include a tert-butyldimethylsilyl group, methoxymethyl group, and tetrahydropyranyl group. Examples of protective groups for an amino group include a tert-butyloxycarbonyl group and benzyloxycarbonyl group. The protective group for a hydroxyl group can be removed by reaction in a solvent such as aqueous methanol, aqueous ethanol, or aqueous tetrahydrofuran in the presence of a base or an acid such as sulfuric acid or acetic acid. A tert-butyldimethylsilyl group can also be removed in a solvent such as tetrahydrofuran in the presence of tetrabutylammonium fluoride, for example. A tert-butyloxycarbonyl group, which is a protective group for an amino group, can be removed, for example, by reaction in a solvent such as aqueous tetrahydrofuran, dichloromethane, chloroform, or aqueous methanol in the presence of an acid such as hydrochloric acid or trifluoroacetic acid. A benzyloxycarbonyl group can be removed, for example, by reaction in a solvent such as acetic acid in the presence of an acid such as hydrobromic acid.

Tert-butyl esters, ortho-esters, acid amides, and the like can be used to protect carboxyl groups. Tert-butyl esters can be removed, for example, by reaction in an aqueous solvent in the presence of hydrochloric acid, ortho-esters can be removed, for example, by treatment in a solvent, such as aqueous methanol, aqueous tetrahydrofuran, or aqueous 1,2-dimethoxyethane, with an acid and then an alkali such as sodium hydroxide. Acid amides can be removed by reaction in a solvent such as water, aqueous

methanol, or aqueous tetrahydrofuran in the presence of an acid such as hydrochloric acid or sulfuric acid.

The compounds represented by Formula (I) include those with optically active centers, and can therefore be obtained in the form of racemates or, when optically active starting materials are used, in the form of optically active isomers. If necessary, racemates that have been obtained can be physically or chemically resolved into optical antipodes by a known method. Diastereomers are preferably formed from the racemates by a reaction using an optical resolution agent. Diastereomers in different form can be resolved by a known method such as fractional crystallization.

The compounds of Formula (I) or prodrugs thereof can be made into salts by, for example, being mixed with a pharmaceutically acceptable acid in a solvent such as water, methanol, ethanol, or acetone. Examples of pharmaceutically acceptable acids include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, or nitric acid; and organic acids such as acetic acid, propionic acid, oxalic acid, succinic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, or ascorbic acid.

Potential applications for the compounds of the present invention are in the treatment of various diseases through their inhibitory action on DPP-IV. The compounds of the present invention are useful for controlling prediabetic postprandial hyperglycemia, treating non-insulin-dependent diabetes, treating autoimmune diseases such as arthritis and rheumatoid arthritis, treating intestinal mucosal diseases, stimulating growth, controlling rejection of organ transplants and grafts, treating obesity, treating eating disorders, treating HIV infection, controlling metastasis, treating prostatic hypertrophy, treating pericementitis, and treating osteoporosis.

When the compounds of the present invention are used for therapeutic purposes, the pharmaceutical composition may be given in oral or parenteral form (such as intravenous, subcutaneous, or intramuscular injection, or local, transrectal, percutaneous, or pernasal administration). Examples of compositions for oral administration include tablets,

capsules, pills, granules, dispersions, liquids, and suspensions. Examples of compositions for parenteral administration include aqueous or oil-based agents for injection, ointments, creams, lotions, aerosols, suppositories, and patches. These agents can be prepared using conventionally known techniques, and can contain nontoxic or inert carriers or excipients commonly used in the pharmaceutical field.

Although the dosage will vary from compound to compound and will depend on the patient's disease, age, weight, gender, symptoms, and the route of administration, the usual dose of the compounds of the invention for adults (50 kg body weight) will be 0.1 to 1000 mg/day, and preferably 1 to 300 mg/day, once a day or divided into two or three portions per day. They may also be given once every few days to every few weeks.

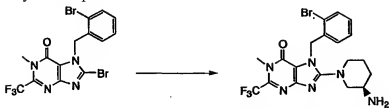
The compounds of the present invention can also be used concomitantly with other agents for the treatment of diabetes.

Examples

The present invention is illustrated in further detail by, but is not limited to, the following reference examples, examples, and test examples. The compounds given in the following reference examples and examples do not always conform to IUPAC nomenclature.

Example 1

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-bromobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



An ethanol (6 mL) solution of (R)-tert-3-butyl piperidin-3-yl carbamate (158 mg), triethylamine (22 μ L), and 8-bromo-7-(2-bromobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one (36 mg) was heated and stirred for 12 hours in a sealed tube at 100°C. The reaction solution was cooled to 25°C, concentrated at reduced pressure, and purified by column chromatography (silica gel, hexane/ethyl acetate = 5/1 to 2/1), giving a product (42 mg). Then, 4N hydrochloric acid/1,4-dioxane solution (20 mL) was added to a 1,4-dioxane solution (2 mL) of the product, and the mixture was stirred for 2.5 hours at

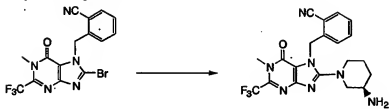
25°C. The solvent was removed by concentration at reduced pressure, and saturated sodium bicarbonate (50 mL) aqueous solution was poured in, followed by extraction with chloroform (30 mL \times 2) and then ethyl acetate (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the titled product (25 mg) was obtained in the form of white solids through purification by preparative thin layer chromatography (silica gel, chloroform/methanol = 10/1).

^1H NMR (300 MHz, CDCl_3) δ ppm 7.62 (d, J = 7.9 Hz, 1H), 7.26–7.15 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 5.53 (s, 2H), 3.68 (s, 3H), 3.57–3.54 (m, 1H), 3.39–3.34 (m, 1H), 3.05–2.95 (m, 2H), 2.85–2.78 (m, 1H), 1.97–1.94 (m, 1H), 1.72–1.58 (m, 2H), 1.37–1.22 (m, 1H).

MS (ESI+) 485 (M^+ +1, 100%).

Example 2

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-cyanobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



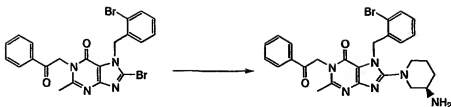
The titled product (21 mg) was obtained in the form of white solids when synthesized in the same manner as in Example 1 using the compound of Reference Example 3 as starting material.

^1H NMR (300 MHz, CDCl_3) δ ppm 7.73 (d, J = 6.8 Hz, 1H), 7.57–7.53 (m, 1H), 7.45–7.40 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 5.72 (s, 2H), 3.66 (s, 3H), 3.50–3.47 (m, 1H), 3.35–3.31 (m, 1H), 3.05–2.96 (m, 2H), 2.80–2.73 (m, 1H), 1.95–1.91 (m, 1H), 1.75–1.61 (m, 2H), 1.28–1.25 (m, 1H).

MS (ESI+) 432 (M^+ +1, 100%).

Example 3

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-bromobenzyl)-1-(2-oxo-2-phenylethyl)-2-methyl-1,7-dihydro-6H-purine-6-one



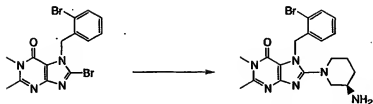
The titled product (55 mg) was obtained in the form of white solids when synthesized in the same manner as in Example 1 using the compound of Reference Example 2 as starting material.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.01 (d, $J = 7.5$ Hz, 1H), 7.66–7.48 (m, 4H), 7.27–7.21 (m, 2H), 7.15–7.10 (m, 1H), 6.82 (d, $J = 7.3$ Hz, 1H), 5.54 (s, 2H), 5.46 (s, 2H), 3.49–3.44 (m, 1H), 3.38–3.33 (m, 1H), 2.99–2.95 (m, 2H), 2.75–2.68 (m, 1H), 2.49 (s, 3H), 1.94–1.88 (m, 1H), 1.68–1.63 (m, 2H), 1.35–1.25 (m, 1H).

MS (ESI+) 535 ($M^+ + 1$, 100%).

Example 4

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-bromobenzyl)-1,2-dimethyl-1,7-dihydro-6H-purine-6-one



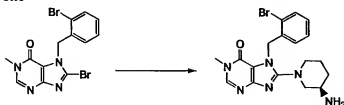
An ethanol (8 mL) solution of (R)-tert-3-butyl piperidin-3-yl carbamate (215 mg) and 8-bromo-7-(2-bromobenzyl)-1,2-dimethyl-1,7-dihydro-6H-purine-6-one (88 mg) was heated and stirred for 25 hours in a sealed tube at 100°C . The reaction solution was cooled to 25°C and then concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, chloroform/methanol = 200/1 to 50/1), giving a product (120 mg). Then, 4N hydrochloric acid/1,4-dioxane solution (20 mL) was added to a 1,4-dioxane solution (2 mL) of the product, and the mixture was stirred for 3 hours at 25°C . The reaction solvent was removed by concentration at reduced pressure, and saturated sodium bicarbonate (50 mL) aqueous solution was poured in, followed by extraction with chloroform (50 mL \times 2) and then ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, giving the titled product (94 mg) in the form of white solids.

^1H NMR (300 MHz, CDCl_3) δ ppm 7.61–7.58 (m, 1H), 7.24–7.12 (m, 2H), 6.77 (d, $J = 7.3$ Hz, 1H), 5.49 (s, 2H), 3.54 (s, 3H), 3.46–3.43 (m, 1H), 3.35–3.30 (m, 1H), 2.97–2.91 (m, 2H), 2.73–2.66 (m, 1H), 2.60 (s, 3H), 1.91–1.83 (m, 1H), 1.69–1.57 (m, 2H), 1.30–1.22 (m, 1H).

MS (ESI+) 431 ($M^+ + 1$, 88%).

Example 5

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-bromobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one



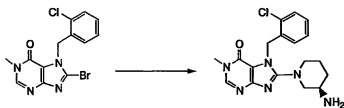
The titled product (86 mg) was obtained in the form of white solids when synthesized in the same manner as in Example 1 using the compound of Reference Example 8 as starting material.

^1H NMR (400 MHz, CDCl_3) δ ppm 8.00 (s, 1H), 7.60 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.25–7.13 (m, 2H), 6.76 (dd, $J = 1.3, 7.6$ Hz, 1H), 5.54 (d, $J = 17.0$ Hz, 1H), 5.50 (d, $J = 17.0$ Hz, 1H), 3.55 (s, 3H), 3.46–3.42 (m, 1H), 3.35–3.30 (m, 1H), 2.98–2.90 (m, 2H), 2.74–2.68 (m, 1H), 1.95–1.85 (m, 1H), 1.74–1.53 (m, 2H), 1.28–1.19 (m, 1H).

MS (ESI+) 417 ($M^+ + 1$, 82%).

Example 6

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one



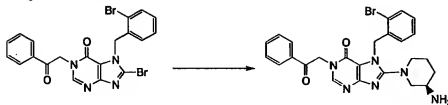
The titled product (87 mg) was obtained in the form of white solids when synthesized

in the same manner as in Example 1 using the compound of Reference Example 7 as starting material.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.02 (s, 1H), 7.40 (dd, J = 1.4, 7.8 Hz, 1H), 7.25-7.16 (m, 2H), 6.79 (dd, J = 1.3, 7.5 Hz, 1H), 5.58 (d, J = 17.0 Hz, 1H), 5.52 (d, J = 17.0 Hz, 1H), 3.55 (s, 3H), 3.52-3.48 (m, 1H), 3.33-3.28 (m, 1H), 3.05-2.95 (m, 2H), 2.82-2.77 (m, 1H), 1.98-1.90 (m, 1H), 1.85-1.57 (m, 2H), 1.37-1.26 (m, 1H).
MS (ESI+) 373 (M⁺+1, 100%).

Example 7

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1,7-dihydro-6H-purine-6-one

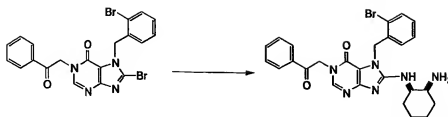


The titled product (90 mg) was obtained in the form of white solids when synthesized in the same manner as in Example 1 using the compound of Reference Example 9 as starting material.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.00-7.98 (m, 2H), 7.93 (s, 1H), 7.63-7.56 (m, 2H), 7.51-7.48 (m, 2H), 7.24-7.22 (m, 1H), 7.15-7.12 (m, 1H), 6.82-6.80 (m, 1H), 5.52 (d, J = 18.0 Hz, 1H), 5.48 (d, J = 18.0 Hz, 1H), 5.40 (s, 2H), 3.48-3.33 (m, 2H), 2.98-2.93 (m, 2H), 2.75-2.69 (m, 1H), 1.92-1.89 (m, 1H), 1.70-1.60 (m, 2H), 1.26-1.23 (m, 1H).
MS (ESI+) 521 (M⁺+1, 88%).

Example 8

8-[(1S)-1-aminocyclohexylamino]-7-(2-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1,7-dihydro-6H-purine-6-one



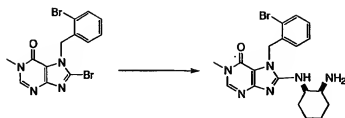
An ethanol (2 mL) solution of cis-1,2-diaminocyclohexane (86 μ L), diisopropylethylamine (50 μ L), and 8-bromo-7-(2-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1,7-dihydro-6H-purine-6-one (75 mg) was heated and stirred for 12 hours in a sealed tube at 100°C. The reaction solution was cooled to 25°C, the solvent was then concentrated at reduced pressure, and chloroform was added to wash the organic layer. The organic layer was then dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure, and the resulting residue was purified on a silica gel column chromatograph (silica gel, chloroform/methanol = 5/1), giving the titled product (6 mg) in the form of light yellow solids.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.98–7.96 (m, 2H), 7.86 (s, 1H), 7.62–7.60 (m, 1H), 7.52–7.43 (m, 3H), 7.26–7.21 (m, 1H), 7.11–7.05 (m, 2H), 5.83 (d, J = 17.0 Hz, 1H), 5.61 (d, J = 17.0 Hz, 1H), 5.40 (s, 2H), 4.60–4.53 (m, 1H), 3.72–3.69 (m, 1H), 3.13–3.08 (m, 1H), 1.98–1.24 (m, 7H).

MS (ESI+) 535 (M⁺+1, 80%).

Example 9

8-[[cis-2-aminocyclohexyl]amino]-7-(2-bromobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one



An N-methyl pyrrolidinone (3 mL) solution of cis-1,2-diaminocyclohexane (0.2 mL), diisopropylethylamine (46 μ L), and 8-bromo-7-(2-bromobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one (70 mg) was heated and stirred for 6 hours in a sealed tube at 160°C. The

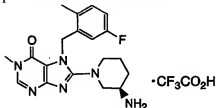
reaction solution was cooled to 25°C, the solvent was then concentrated at reduced pressure, and chloroform was added to wash the organic layer. The organic layer was then dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure, and the resulting residue was purified on a silica gel column chromatograph (silica gel, chloroform/methanol = 10/1 to chloroform/methanol/triethylamine = 10/1/0.1), giving the titled product (71 mg) in the form of light yellow solids.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.92 (s, 1H), 7.59–7.57 (m, 1H), 7.24–7.21 (m, 1H), 7.19–7.16 (m, 1H), 6.97–6.94 (m, 1H), 5.67 (d, J = 16.0 Hz, 1H), 5.60 (d, J = 16.0 Hz, 1H), 5.23–5.17 (m, 1H), 4.13–4.11 (m, 1H), 3.56 (s, 3H), 3.23–3.21 (m, 1H), 1.76–1.26 (m, 7H).

MS (ESI+) 431 (M⁺+1, 100%).

Example 10

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-methyl-5-fluorobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one trifluoroacetate



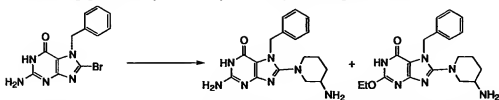
The compound of Reference Example 14 was synthesized as the starting material in the same manner as in Reference Example 2, and the resulting product was synthesized in the same manner as in Example 1. The reaction product was purified by liquid chromatography (HPLC), giving the titled product (21 mg) in the form of white solids.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.99 (s, 1H), 7.16–7.13 (m, 1H), 6.88–6.84 (m, 1H), 6.40–6.37 (m, 1H), 5.42 (d, J = 17.0 Hz, 1H), 5.37 (d, J = 17.0 Hz, 1H), 3.53 (s, 3H), 3.48–3.44 (m, 1H), 3.34–3.30 (m, 1H), 2.98–2.93 (m, 2H), 2.78–2.73 (m, 1H), 2.34 (s, 3H), 1.92–1.87 (m, 1H), 1.71–1.59 (m, 2H), 1.26–1.23 (m, 1H).

MS (ESI+) 371 (M⁺+1, 100%).

Example 11

2-amino-8-(3-aminopiperidin-1-yl)-7-benzyl-1,7-dihydro-6H-purine-6-one and 2-ethoxy-8-(3-aminopiperidin-1-yl)-7-benzyl-1,7-dihydro-6H-purine-6-one



Sodium sulfite (323 mg) was added to an ethanol (10 mL) solution of concentrated sulfuric acid (0.4 mL) and 2-amino-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one (500 mg), and the mixture was stirred for 2 hours while heated to reflux. Water (50 mL) and saturated sodium bicarbonate aqueous solution (20 mL) were added, and the precipitated crystals were filtered off and dried at reduced pressure. The resulting solids were then suspended in N-methylpyrrolidinone (10 mL), 3-aminopiperidine dihydrochloride (500 mg) and diisopropylethylamine (1.6 mL) were added, and the mixture was stirred for 30 hours in a sealed tube at 110°C. The reaction solution was cooled to 25°C, and 2N-hydrochloric acid aqueous solution (30 mL) was then added, followed by extraction with ethyl acetate (50 mL). Potassium carbonate was added to the aqueous layer, rendering it alkaline, and the precipitated solids were filtered off. Chloroform (30 mL) was added to the filtrate, the precipitated crystals were filtered off, and the crystals were washed with methanol (10 mL) and dried, giving 2-amino-8-(3-aminopiperidin-1-yl)-7-benzyl-1,7-dihydro-6H-purine-6-one (48 mg). The above chloroform layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, chloroform/methanol = 10/1 to chloroform/methanol/triethylamine = 10/1/0.1), giving 2-ethoxy-8-(3-aminopiperidin-1-yl)-7-benzyl-1,7-dihydro-6H-purine-6-one (10 mg).

2-amino-8-(3-aminopiperidin-1-yl)-7-benzyl-1,7-dihydro-6H-purine-6-one:

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.32-7.14 (m, 5H), 6.05 (s, 2H), 5.30 (d, J = 15.9 Hz, 1H), 5.26 (d, J = 15.9 Hz, 1H), 3.43-3.17 (m, 2H), 2.80-2.67 (m, 2H), 2.57-2.46 (m, 1H), 1.84-1.76 (m, 1H), 1.72-1.60 (m, 1H), 1.59-1

.45 (m, 1H), 1.20–1.07 (m, 1H).

MS (ESI+) 340 ($M^+ + 1$, 45%).

2-ethoxy-8-(3-aminopiperidin-1-yl)-7-benzyl-1,7-dihydro-6H-purine-6-one:

^1H NMR (400 MHz, CD_3OD) δ ppm 7.34–7.17 (m, 5H), 5.47 (d, $J = 15.6$ Hz, 1H), 5.42 (d, $J = 15.6$ Hz, 1H), 4.44 (q, $J = 7.1$ Hz, 2H), 3.58–3.52 (m, 1H), 3.28–3.15 (m, 2H), 2.98–2.88 (m, 2H), 2.06–1.98 (m, 1H), 1.83–1.73 (m, 1H), 1.70–1.58 (m, 1H), 1.55–1.43 (m, 1H), 1.40 (t, $J = 7.1$ Hz, 3H).

MS (ESI+) 369 ($M^+ + 1$, 100%).

Example 12

2-dimethylamino-8-[(3R)-3-aminopiperidin-1-yl]-7-benzyl-1-methyl-1,7-dihydro-6H-purine-6-one



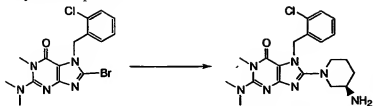
An ethanol (5 mL) suspension of diisopropylethylamine (0.26 mL), (R)-3-aminopiperidine dihydrochloride (53 mg), and 1-methyl-2-dimethylamino-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one (55 mg) was heated and stirred for 100 hours at 110°C. The reaction solution was cooled to 25°C and then concentrated at reduced pressure, and saturated brine was added to the residue for extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure, giving the titled product (61 mg).

^1H NMR (400 MHz, CDCl_3) δ ppm 7.40–7.18 (m, 5H), 5.46 (d, $J = 15.7$ Hz, 1H), 5.39 (d, $J = 15.7$ Hz, 1H), 3.52 (s, 3H), 3.56–3.46 (m, 1H), 3.32–3.25 (m, 1H), 2.83 (s, 6H), 3.12–2.78 (m, 3H), 2.01–1.92 (m, 1H), 1.80–1.70 (m, 1H), 1.69–1.57 (m, 1H), 1.43–1.33 (m, 1H).

MS (ESI+) 382 ($M^+ + 1$, 100%).

Example 13

2-dimethylamino-8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one



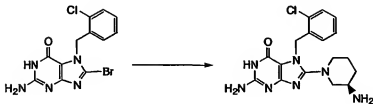
The titled product (34 mg) was obtained in the form of a brown oil when synthesized in the same manner as in Example 12 using the compound of Reference Example 6 as starting material.

^1H NMR (400 MHz, CDCl_3) δ ppm 7.42–7.37 (m, 1H), 7.23–7.13 (m, 2H), 6.81 (m, 1H), 5.52 (d, $J = 17.1$ Hz, 1H), 5.48 (d, $J = 17.1$ Hz, 1H), 3.51 (s, 3H), 3.45–3.39 (m, 1H), 3.34–3.26 (m, 1H), 2.97–2.87 (m, 2H), 2.86 (s, 6H), 2.72–2.65 (m, 1H), 1.93–1.84 (m, 1H), 1.73–1.53 (m, 2H), 1.28–1.17 (m, 1H).

MS (ESI+) 416 ($M^+ + 1$, 100%).

Example 14

2-amino-8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1,7-dihydro-6H-purine-6-one



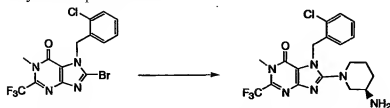
The titled product (83 mg) was obtained in the form of a brown oil when synthesized in the same manner as in Example 12 using the compound of Reference Example 11 as starting material.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.50–7.45 (m, 1H), 7.36–7.23 (m, 2H), 6.72–6.67 (m, 1H), 6.10 (s, 2H), 5.32 (s, 2H), 3.40–3.25 (m, 1H), 3.18–3.10 (m, 1H), 2.77–2.60 (m, 2H), 2.56–2.47 (m, 1H), 1.79–1.70 (m, 1H), 1.63–1.53 (m, 1H), 1.48–1.34 (m, 1H), 1.15–1.03 (m, 1H).

MS (ESI+) 374 ($M^+ + 1$, 100%).

Example 15

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



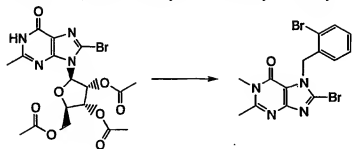
The titled product (53 mg) was obtained in the form of white solids when synthesized in the same manner as in Example 1 using the compound of Reference Example 25 as starting material.

^1H NMR (300 MHz, CDCl_3) δ ppm 7.45–7.42 (m, 1H), 7.26–7.18 (m, 2H), 6.80 (d, $J = 7.5$ Hz, 1H), 5.57 (s, 2H), 3.68 (d, $J = 1.3$ Hz, 3H), 3.51–3.48 (m, 1H), 3.41–3.37 (m, 1H), 3.05–2.91 (m, 2H), 2.77–2.70 (m, 1H), 1.90–1.88 (m, 1H), 1.71–1.58 (m, 2H), 1.28–1.25 (m, 1H).

MS (ESI+) 441 ($\text{M}^+ + 1$, 100%).

Reference Example 1

8-bromo-7-(2-bromobenzyl)-1,2-dimethyl-1,7-dihydro-6H-purine-6-one



A mixture of 2',3',5'-tri-0-(acetoxymethyl)-2-methyl-8-bromoinosine (393 mg), 85% phosphoric acid aqueous solution (160 μL), and acetic anhydride (4 mL) was mixed for 1.5 hours at 100°C. The mixture was then cooled to 25°C, and the precipitated solids were filtered off. The solids were washed with chloroform and then dried at reduced pressure, giving a deribosylated compound (0.427 g). The spectrum of the compound is given below.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 12.30 (bs, 1H), 2.34 (s, 3H).

MS (ESI+) 229 (M^+ , 100%).

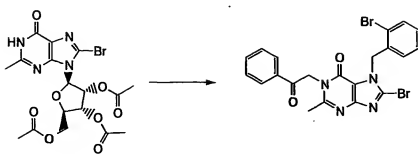
The deribosylated compound (0.701 g) was then dissolved in *N,N*-dimethyl formamide (20 mL) at 25°C, sodium bicarbonate (390 mg) was added to the resulting solution, and the mixture was stirred over night. Potassium carbonate (270 mg) and 2-bromobenzyl bromide (390 mg) were also added, and the mixture was stirred for 7 hours. Toluene (20 mL) was added to the reaction solution for concentration at reduced pressure (4 times), and saturated sodium bicarbonate aqueous solution (50 mL) was added to the residue, followed by extraction twice with ethyl acetate (100 mL). The organic layer was concentrated at reduced pressure, and the precipitated solids were filtered and washed with toluene and thoroughly dried, giving a crude product (250 mg). Sodium hydride (30 mg, 60% oil dispersion) was added to an *N,N*-dimethyl formamide (10 mL) solution of the crude product (250 mg) at 25°C, the mixture was stirred for 15 minutes, methyl iodide (195 μL) was added, and the mixture was stirred for 4 hours at 25°C. Saturated sodium bicarbonate aqueous solution (10 mL) was poured into the reaction solution, toluene (20 mL) was then added for concentration at reduced pressure (twice), and saturated sodium bicarbonate aqueous solution (40 mL) was added to the residue for extraction twice with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1/2 to 3/1), giving the titled product (88 mg).

^1H NMR (300 MHz, CDCl_3) δ ppm 7.63–7.60 (m, 1H), 7.20–7.13 (m, 2H), 6.43–6.40 (m, 1H), 5.74 (s, 2H), 3.57 (s, 3H), 2.65 (s, 3H).

MS (ESI+) 411 (M^+ +1, 57%).

Reference Example 2

8-bromo-7-(2-bromobenzyl)-1-(2-oxo-2-phenylethyl)-2-methyl-1,7-dihydro-6H-purine-6-one



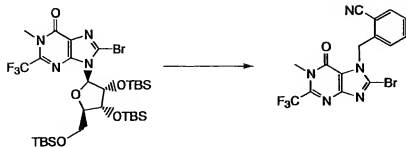
A mixture of 2',3',5'-tri-O-(acetoxy)-2-methyl-8-bromoinosine (1.052 g), 85% phosphoric acid aqueous solution (440 μ L), and acetic anhydride (10 mL) was mixed for 1.5 hours at 100°C. The mixture was then cooled to 25°C, and the precipitated solids were filtered off. The solids were washed with chloroform and then dried at reduced pressure, giving a deribosylated compound (1.157 g).

The deribosylated compound (1.157 g) was then dissolved in N,N-dimethyl formamide (30 mL) at 25°C, potassium bicarbonate (896 mg) and 2-bromobenzyl bromide (670 mg) were added to the resulting solution, and the mixture was stirred over night. Toluene (20 mL) was added to the reaction solution for concentration at reduced pressure (4 times), and saturated sodium bicarbonate aqueous solution (50 mL) was added to the residue, followed by extraction twice with ethyl acetate (100 mL). The organic layer was concentrated at reduced pressure, and the precipitated solids were filtered and washed with toluene and thoroughly dried, giving a crude product (200 mg). Sodium hydride (24 mg, 60% oil dispersion) was added to an N,N-dimethyl formamide (10 mL) solution of the crude product (200 mg) at 25°C, the mixture was stirred for 30 minutes, α -bromoacetophenone (110 mg) was then added, and the mixture was stirred over night at 25°C. Saturated sodium bicarbonate aqueous solution (10 mL) was poured into the reaction solution, followed by concentration at reduced pressure, and saturated sodium bicarbonate aqueous solution (50 mL) was added to the residue for extraction twice with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1/5 to 3/1), giving the titled product (61 mg).

¹H NMR (300 MHz, CDCl₃) δ ppm 8.03-8.00 (m, 2H), 7.68-7.49 (m, 4H), 7.22-7.12 (m, 2H), 6.48-6.45 (m, 1H), 5.70 (s, 2H), 5.56 (s, 2H), 2.52 (s, 3H).
MS (ESI+) 517 (M⁺+1, 100%).

Reference Example 3

8-bromo-7-(2-cyanobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



A mixture of 2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-1-methyl-2-trifluoromethyl-8-bromoinosine (244 mg) was used as starting material to synthesize the deribosylated form (268 g) in the same manner as in Reference Example 1. The spectrum of the compound is given below.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 3.75 (d, $J = 1.3$ Hz, 3H).

MS (ESI+) 297 ($M^+ + 1$, 81%).

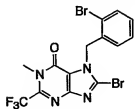
The deribosylated compound (268 mg) was then dissolved in N,N -dimethyl formamide (10 mL) at 25°C , potassium bicarbonate (437 mg) and 2-bromobenzyl bromide (248 mg) were added, and the mixture was heated to 80°C and stirred for 4 hours. Toluene (20 mL) was added to the reaction solution for concentration at reduced pressure (repeated 3 times), and saturated sodium bicarbonate aqueous solution (50 mL) was added to the residue, followed by extraction twice with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1/5 to 1/1), giving the titled product (58 mg).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.77-7.40 (m, 3H), 6.88 (d, $J = 7.9$ Hz, 1H), 5.94 (s, 2H), 3.75 (s, 3H).

MS (ESI+) 412 ($M^+ + 1$, 99%).

Reference Example 4

8-bromo-7-(2-bromobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



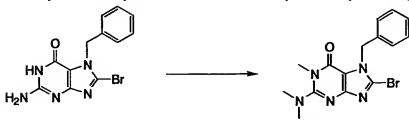
The compound of Reference Example 23 was used as starting material for synthesis in the same manner as in Reference Example 2, giving the titled compound (36 mg) in the form of white solids.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.65-7.62 (m, 1H), 7.24-7.14 (m, 2H), 6.45-6.41 (m, 1H), 5.78 (s, 2H), 3.72 (d, $J = 1.3$ Hz, 3H).

MS (ESI+) 465 ($M^+ + 1$, 46%).

Reference Example 5

1-methyl-2-dimethylamino-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one



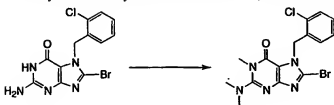
Sodium hydride (150 mg, 60% oil dispersion) was added to an N,N-dimethyl formamide (3 mL) suspension of 2-amino-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one (300 mg) at room temperature, and the suspension was stirred for 1 hour. Methyl iodide (0.3 mL) was added, the mixture was stirred for 5 hours at the same temperature, and iced water was then added to the reaction mixture for extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 1/1 to ethyl acetate), giving the target product (55 mg).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.38–7.25 (m, 5H), 5.58 (s, 2H), 3.55 (s, 3H), 2.86 (s, 6H).

MS (ESI+) 362 ($\text{M}^+ + 1$, 92%).

Reference Example 6

1-methyl-2-dimethylamino-8-bromo-7-(2-chlorobenzyl)-1,7-dihydro-6H-purine-6-one



Sodium hydride (118 mg, 60% oil dispersion) was added to an N,N-dimethyl formamide (2 mL) suspension of 2-amino-8-bromo-7-(2-chlorobenzyl)-1,7-dihydro-6H-purine-6-one (300 mg) at room temperature, and the suspension was stirred for 1 hour. Methyl iodide (0.26 mL) was added, the mixture was stirred for 5 hours at the same temperature, and iced water was then added to the reaction mixture for extraction with

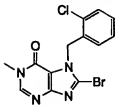
ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 1/1), giving the target product (67 mg).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.43–7.40 (m, 1H), 7.25–7.11 (m, 2H), 6.54–6.52 (m, 1H), 5.73 (s, 2H), 3.52 (s, 3H), 2.89 (s, 6H).

$\text{MS (ESI}^+) \text{ 398 (M}^+ + 1, 100\%)$.

Reference Example 7

8-bromo-7-(2-chlorobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one



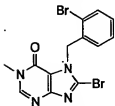
The compound of Reference Example 14 was used as starting material and 2-chlorobenzyl bromide was used for synthesis in the same manner as in Reference Example 2, giving the titled compound (130 mg) in the form of white solids.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 8.07 (s, 1H), 7.43–7.42 (m, 1H), 7.26–7.22 (m, 1H), 7.16–7.13 (m, 1H), 6.51–6.49 (m, 1H), 5.79 (s, 2H), 3.59 (s, 3H).

$\text{MS (ESI}^+) \text{ 352 (M}^+, 66\%)$.

Reference Example 8

8-bromo-7-(2-bromobenzyl)-1-methyl-1,7-dihydro-6H-purine-6-one



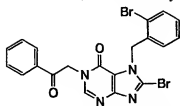
The compound of Reference Example 14 was used as starting material for synthesis in the same manner as in Reference Example 2, giving the titled compound (164 mg) in the form of white solids.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 8.07 (s, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.21–

7.14 (m, 2H), 6.43 (d, $J = 7.3$ Hz, 1H), 5.63 (s, 2H), 3.59 (s, 3H).
 MS (ESI+) 396 ($M^+ + 1$, 51%).

Reference Example 9

8-bromo-7-(2-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1,7-dihydro-6H-purine-6-one



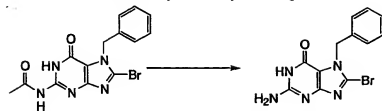
The compound of Reference Example 15 was used as starting material for synthesis in the same manner as in Reference Example 2, giving the titled compound (215 mg) in the form of white solids.

^1H NMR (400 MHz, CDCl_3) δ ppm 8.02–7.99 (m, 2H), 7.98 (s, 1H), 7.67–7.64 (m, 1H), 7.61–7.59 (m, 1H), 7.54–7.50 (m, 2H), 7.22–7.20 (m, 1H), 7.20–7.15 (m, 1H), 6.49–6.47 (m, 1H), 5.74 (s, 2H), 5.43 (s, 2H).

MS (ESI+) 501 ($M^+ + 1$, 62%).

Reference Example 10

2-amino-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one

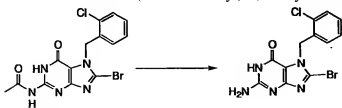


2-acetyl-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one (2.23 g) was suspended in 30% methylamine-ethanol solution (100 mL), and the mixture was stirred for 15 hours at room temperature. Approximately half of the solvent was distilled off, water (200 mL) was added, and the resulting crystals were filtered off and dried at reduced pressure, giving the titled product (1.88 g).

MS (ESI+) 320 ($M^+ + 1$, 100%).

Reference Example 11

2-amino-8-bromo-7-(2-chlorobenzyl)-1,7-dihydro-6H-purine-6-one

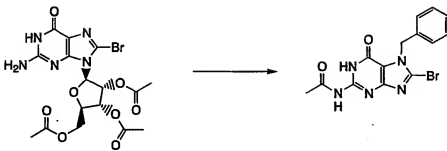


The compound of Reference Example 13 was used as starting material for synthesis in the same manner as in Reference Example 10, giving the titled compound (1.16 g) in the form of white solids.

MS (ESI+) 354 ($M^+ + 1$, 75%).

Reference Example 12

2-acetylamino-8-bromo-7-benzyl-1,7-dihydro-6H-purine-6-one



A mixture of 2',3',5'-tri-O-acetyl-8-bromoguanosine (36.20 g), 85% phosphoric acid aqueous solution (1.5 mL), and acetic anhydride (400 mL) was stirred for 1.5 hours at 100°C. The mixture was then cooled to 25°C, and the precipitated crystals were filtered off. The crystals were washed with chloroform and then dried at reduced pressure, giving a product (18.23 g). The spectrum of the product is given below.

MS (ESI+) 272 ($M^+ + 1$, 100%).

Benzyl bromide (22.9 g) was added to an N,N-dimethyl formamide (500 mL) suspension of the product (18.23 g). The reaction solution was stirred for 10 hours at 100°C. The reaction solution was cooled to 25°C, and water (500 mL) and chloroform (500 mL) were then added. The insoluble material was filtered off, followed by concentration at reduced pressure. The residue was purified by column chromatography

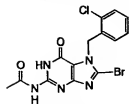
(silica gel, chloroform/methanol = 50/1 to 20/1, chloroform/ethyl acetate = 1/1), giving the titled product (3.31 g).

$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.22 (s, 1H), 11.71 (s, 1H), 7.38–7.25 (m, 5H), 5.54 (s, 2H), 2.16 (s, 3H).

MS (ESI+) 362 ($M^+ + 1$, 100%).

Reference Example 13

2-acetylamino-8-bromo-7-(2-chlorobenzyl)-1,7-dihydro-6H-purine-6-one



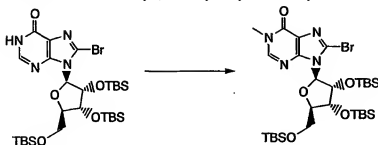
The titled compound (1.80 g) was obtained in the form of white solids by synthesis in the same manner as in Reference Example 12.

$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.20 (s, 1H), 11.74 (s, 1H), 7.57–7.53 (m, 1H), 7.38–7.25 (m, 2H), 6.61–6.57 (m, 1H), 5.62 (s, 2H), 2.17 (s, 3H).

MS (ESI+) 396 ($M^+ + 1$, 65%).

Reference Example 14

2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-1-methyl-8-bromoinosine



Sodium hydride (0.13 g, 60% oil dispersion) was added to a tetrahydrofuran (30 mL) solution of 2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-8-bromoinosine (2.0 g) while cooled on ice, and the mixture was stirred for 30 minutes. Methyl iodide (0.70 mL) was added to the reaction solution, the mixture was stirred for 4 hours at 25°C, and water was then

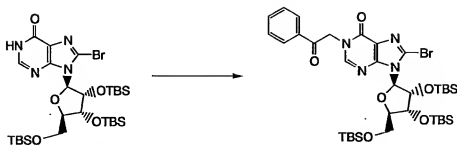
added. After extraction with chloroform, the organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate. The residue obtained upon filtration and concentration at reduced pressure was purified by silica gel column chromatography (silica gel, hexane/ethyl acetate = 3/1 to 1/1), giving the titled compound (1.8 g).

¹H NMR (400 MHz, CDCl₃) δ ppm 7.89 (s, 1H), 5.95 (d, J = 6.0 Hz, 1H), 5.2 3-5.20 (m, 1H), 4.51-4.49 (m, 1H), 4.08-4.05 (m, 1H), 3.98-3.95 (m, 1H), 3.73-3.71 (m, 1H), 3.65 (s, 3H), 0.91 (s, 9H), 0.85 (s, 9H), 0.81 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H), -0.05 (s, 3H), -0.30 (s, 3H).

MS (ESI+) 703 (M⁺+1, 85%).

Reference Example 15

2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-1-(2-oxo-2-phenylethyl)-8-bromoinosine



Sodium hydride (0.13 g, 60% oil dispersion) was added to a tetrahydrofuran (30 mL) solution of 2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-8-bromoinosine (2.0 g) while cooled on ice, and the mixture was stirred for 30 minutes. α-bromoacetophenone (0.61 g) was added to the reaction solution, the mixture was stirred for 6 hours at 25°C, and water was then added. After extraction with ethyl acetate, the organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate. The residue obtained upon filtration and concentration at reduced pressure was purified by silica gel column chromatography (silica gel, hexane/ethyl acetate = 5/1 to 2/1), giving the titled compound (2.3 g).

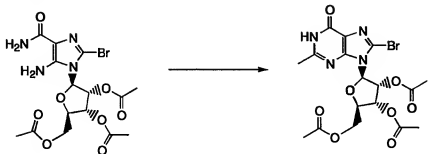
¹H NMR (400 MHz, CDCl₃) δ ppm 8.05-8.03 (m, 2H), 7.83 (s, 1H), 7.69-7.65 (m, 1H), 7.56-7.52 (m, 2H), 5.99 (d, J = 6.0 Hz, 1H), 5.69 (d, J = 17.0 Hz, 1H), 5.36 (d, J = 17.0 Hz, 1H), 5.27-5.25 (m, 1H), 4.52-4.50 (m, 1H), 4.08-4.05 (m, 1H), 4.00-3.98 (m, 1H), 3.77-3.73 (m, 1H), 0.96 (s, 9H), 0.86

(s, 9H), 0.82 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), -0.02 (s, 3H), -0.25 (s, 3H).

MS (ESI+) 807 ($M^+ + 1$, 83%).

Reference Example 16

2',3',5'-tri-O-(acetoxy)-2-methyl-8-bromoinosine



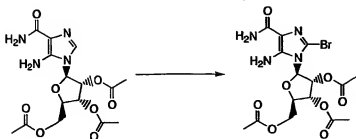
An acetic acid (3 mL) solution of triethyl ortho-acetate (1.82 mL) was added to an N,N-dimethyl formamide (3 mL) solution of 2-bromo-5-aminoimidazole-4-carboxyamido-2,3,5-tri-O-acetyl-1- β -D-ribofuranoside (463 mg), and the mixture was heated and stirred for 4 hours at 80 to 100°C. The reaction solution was cooled to 25°C, and toluene (20 mL) was then added for concentration at reduced pressure (4 times), giving a product [MS (ESI+) 533 ($M^+ + 1$, 97%)]. Potassium tert-butoxide (168 mg) was then added to a tetrahydrofuran (10 mL) solution of the product, and the mixture was stirred for 2 hours at 25°C. Water (10 mL) was poured into the reaction solution, and the solution was concentrated at reduced pressure. Saturated brine (30 mL) was added to the residue, followed by extraction 3 times with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The residue was purified by column chromatography (silica gel, chloroform/methanol = 200/1 to 40/1), giving the titled compound (282 g).

^1H NMR (300 MHz, CDCl_3) δ ppm 13.22 (s, 1H), 6.19 (dd, $J = 4.0, 5.9$ Hz, 1H), 6.08 (d, $J = 3.8$ Hz, 1H), 5.96 (t, $J = 6.0$ Hz, 1H), 4.52-4.47 (m, 1H), 4.43-4.38 (m, 1H), 4.34-4.28 (m, 1H), 2.64 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H).

MS (ESI+) 487 ($M^+ + 1$, 85%).

Reference Example 17

2-bromo-5-aminoimidazole-4-carboxyamido-2,3,5-tri-O-acetyl-1-β-D-ribofuranoside



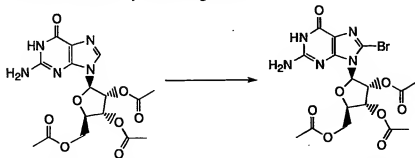
A tetrahydrofuran (100 mL) solution of N-bromoacetoamide (6.05 g) was gradually added to a tetrahydrofuran (100 mL) solution of 5-aminoimidazole-4-carboxyamido-2,3,5-tri-O-acetyl-1-β-D-ribofuranoside (19.52 g) at -5°C in a nitrogen atmosphere, and the ingredients were stirred for 1.5 hours at 25°C. Water (100 mL) was poured in, followed by the removal of the tetrahydrofuran at reduced pressure and extraction with chloroform (100 mL × 3). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, chloroform/methanol = 200/1 to 40/1), giving the titled product (10.39 g).

¹H NMR (300 MHz, CDCl₃) δ ppm 6.44 (bs, 1H), 5.93 (d, J = 7.1 Hz, 1H), 5.66–5.61 (m, 1H), 5.56 (s, 2H), 5.40–5.37 (m, 1H), 5.22 (bs, 1H), 4.62 (dd, J = 2.6, 12.1 Hz, 1H), 4.33–4.25 (m, 2H), 2.17 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H).

MS (ESI+) 463 (M⁺+1, 86%).

Reference Example 18

2',3',5'-tri-O-acetoxy-8-bromoguanosine



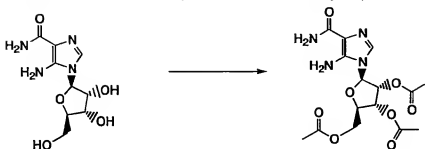
A solution consisting of bromine (5 mL) and water (500 mL) was injected in a total of

10 portions to an aqueous (1000 mL) suspension of 2',3',5'-tri-O-acetyl guanosine (37.93 g), and the mixture was stirred for 20 minutes at 25°C. The resulting crystals were filtered off and dried at reduced pressure, giving the target product (36.20 g).

MS (ESI+) 488 (M^+ +1, 100%).

Reference Example 19

5-aminoimidazole-4-carboxyamido-2,3,5-tri-O-acetyl-1-β-D-ribofuranoside

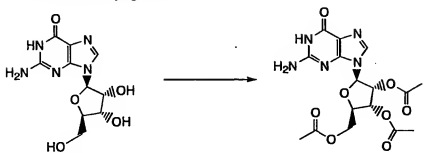


A suspension of 5-aminoimidazole-4-carboxyamido-1-β-D-ribofuranoside (10.30 g), acetic anhydride (14.70 g), and triethylamine (21.90 g) was heated and stirred for 4 hours in a nitrogen atmosphere in a sealed tube at 50°C. The reaction solution was cooled to 25°C, and toluene (100 mL) was then added for concentration at reduced pressure (repeated 3 times), giving a crude product (19.52 g).

MS (ESI+) 385 (M^+ +1, 100%).

Reference Example 20

2',3',5'-tri-O-acetyl guanosine



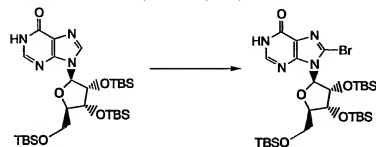
4-(dimethylamino)pyridine (0.92 g), triethylamine (55.7 mL), and acetic anhydride (34 mL) were added at room temperature to an acetonitrile (1250 mL) suspension of

guanosine (28.32 g), and the mixture was stirred for 30 minutes. Methanol (20 mL) was added, the ingredients were stirred for 5 minutes, the solvent was distilled off at reduced pressure, 2-propanol (300 mL) was added to the residue for extraction, which was dried at reduced pressure, giving the product (37.93 g).

MS (ESI+) 410 ($M^+ + 1$, 100%).

Reference Example 21

2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-8-bromoinosine



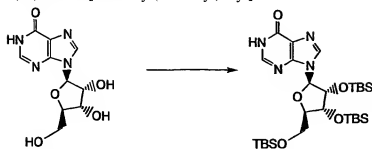
A tetrahydrofuran (8 mL) solution of diisopropylethylamine (3.2 mL) was cooled on ice, and n-butyl lithium (1.58 M hexane solution, 15 mL) was added in the form of drops. The contents were then stirred for 15 minutes, and the reaction solution was cooled to -78°C. A tetrahydrofuran (20 mL) solution of 2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]inosine (5.0 g) was added in the form of drops over a period of 10 minutes, and the contents were then stirred for 1 hour. Dibromotetrafluoroethane (2.9 mL) was added in the form of drops to the reaction solution at -78°C, and the contents were then stirred for 2 hours. Saturated ammonium chloride aqueous solution was added to the reaction solution before chloroform extraction. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. Upon filtration and subsequent concentration at reduced pressure, the residue was purified by silica gel column chromatography (silica gel, hexane/ethyl acetate = 3/1 to 1/1), giving the target product (4.8 g) in the form of light yellow solids.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 13.21 (s, 1H), 8.33 (s, 1H), 5.96 (d, $J = 5.0$ Hz, 1H), 5.30–5.32 (m, 1H), 4.46–4.45 (m, 1H), 4.04–3.98 (m, 1H), 3.98–3.96 (m, 1H), 3.72–3.69 (m, 1H), 0.93 (s, 9H), 0.83 (s, 9H), 0.77 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H), -0.08 (s, 3H), -0.34 (s, 3H).

MS (ESI+) 689 ($M^+ + 1$, 76%).

Reference Example 22

2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]inosine



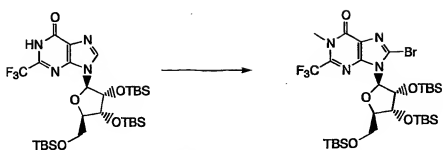
Tert-butyldimethylchlorosilane (76.6 g) and imidazole (69.3 g) were added to an N,N-dimethyl formamide (600 mL) solution of (-)-inosine (22.7 g), and the resulting solution was stirred for 18 hours at 25°C. Water was added to the reaction solution before extraction with chloroform. The organic layer was washed with water and saturated brine, and was dried over anhydrous magnesium sulfate. Upon filtration and subsequent concentration at reduced pressure, the resulting residue was purified by silica gel column chromatography (silica gel, hexane/ethyl acetate = 3/1 to chloroform/methanol = 10/1), giving the target product (50.2 g).

^1H NMR (400 MHz, CDCl_3) δ ppm 8.24 (s, 1H), 8.11 (s, 1H), 6.01 (d, J = 5.0 Hz, 1H), 4.51–4.49 (m, 1H), 4.31–4.29 (m, 1H), 4.14–4.12 (m, 1H), 4.02–3.98 (m, 1H), 3.81–3.78 (m, 1H), 0.96 (s, 9H), 0.93 (s, 9H), 0.81 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), -0.01 (s, 3H), -0.18 (s, 3H).

MS (ESI+) 611 (M^+ +1, 100%).

Reference Example 23

2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-1-methyl-2-trifluoromethyl-8-bromoinosine



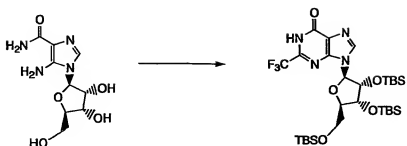
Tert-butyl lithium (1.50 M pentane solution, 2.6 mL) was gradually added in the form of drops to a tetrahydrofuran (20 mL) solution of 2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-1-methyl-2-trifluoromethyl inosine in a nitrogen atmosphere, and the ingredients were stirred for 1.5 hours. The solution was cooled to -78°C , a tetrahydrofuran (2 mL) solution of 1,2-dibromo-1,1,2,2-tetrafluoroethane (617 μL) was gradually added in the form of drops, and the ingredients were stirred for 1 hour. The temperature was then increased to 25°C over a period of 5 hours. Saturated ammonium chloride aqueous solution (10 mL) was poured in, the reaction solution was then concentrated at reduced pressure, and saturated sodium bicarbonate aqueous solution (100 mL) was added to the residue before extraction twice with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, giving a crude product (981 mg). In a nitrogen atmosphere, sodium hydride (62 mg) was added to an N,N-dimethyl formamide (15 mL) solution of the crude product (981 mg), the ingredients were stirred for 30 minutes at 25°C , methyl iodide (404 μL) was then added in the form of drops, and the ingredients were stirred over night at 25°C . Saturated ammonium chloride aqueous solution (2 mL) was poured in, the reaction solution was then concentrated at reduced pressure, and saturated sodium bicarbonate aqueous solution (50 mL) was added to the residue before extraction twice with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the residue was purified by silica gel column chromatography (silica gel, hexane/ethyl acetate = 200/1 to 10/1), giving the target product (398 mg).

^1H NMR (300 MHz, CDCl_3) δ ppm 6.02 (d, $J = 6.9$ Hz, 1H), 5.20 (dd, $J = 4.4$, 7.0 Hz, 1H), 4.35–4.34 (m, 1H), 4.08–4.03 (m, 1H), 3.91–3.84 (m, 1H), 3.79 (s, 3H), 3.73–3.65 (m, 1H), 0.96 (s, 9H), 0.89 (s, 9H), 0.78 (s, 9H), 15–0.02 (m, 12H), -0.08 (s, 3H), -0.34 (s, 3H).

MS (ESI+) 771 ($\text{M}^+ + 1$, 81%).

Reference Example 24

2',3',5'-tri-O-[tert-butyl(dimethyl)silyl]-2-trifluoromethylinosine



A 21 wt% sodium ethoxide/ethanol solution (15 mL) was gradually added to an ethanol (15 mL) solution of 5-aminoimidazole-4-carboxyamido-1- β -D-ribofuranoside (1.03 g) in a nitrogen atmosphere, and the ingredients were stirred for 30 minutes at 25°C. Ethyl trifluoroacetate (4.8 mL) was then gradually added, and the ingredients were heated and stirred for 8 hours at 80°C. After being cooled to 25°C, the reaction solution was neutralized with 2N hydrochloric acid to adjust the pH to 5, and saturated sodium bicarbonate aqueous solution was then added to adjust the pH to 8. The reaction solvent was distilled off at reduced pressure, water was added, and the precipitated solids were filtered off and washed with toluene. They were thoroughly dried at reduced pressure, giving a crude product (0.93 g). Imidazole (2.26 g), tert-butyl dimethyl chlorosilane (2.50 g), and 4-(dimethylamino)pyridine (100 mg) were added to a N,N-dimethyl formamide (20 mL) solution of the crude product (0.93 g), and the mixture was stirred over night at 25°C. The reaction solvent was distilled off at reduced pressure, and saturated sodium bicarbonate aqueous solution (80 mL) was added before extraction twice with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The residue was then again made into an N,N-dimethyl formamide solution (20 mL), and imidazole (2.26 g), tert-butyl dimethyl chlorosilane (2.50 g), and 4-(dimethylamino)pyridine (100 mg) were added before the solution was again stirred over night at 25°C. The reaction solvent was distilled off at reduced pressure, and saturated sodium bicarbonate aqueous solution (80 mL) was added before extraction twice with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and then concentrated at reduced pressure, and the residue was purified by column chromatography (silica gel, chloroform/methanol = 100/1 to 25/1), giving the target product (1.83 g).

¹H NMR (300 MHz, CDCl₃) δ ppm 8.37 (s, 1H), 5.99 (d, J = 4.4 Hz, 1H), 4.54 (t, J = 4.2 Hz, 1H), 4.31 (t, J = 4.2 Hz, 1H), 4.16–4.15 (m, 1H), 4.06–4.01 (m, 1H), 3.83–3.78 (m, 1H), 0.96 (s, 9H), 0.93 (s, 9H), 0.83 (s, 9H), 0.17–0.07 (m, 12H), 0.00 (s, 3H), -0.15 (s, 3H).

MS (ESI+) 679 ($M^+ + 1$, 100%).

Reference Example 25

8-bromo-7-(2-chlorobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



The compound (530 mg) of Reference Example 26 was used as starting material for synthesis in the same manner as in Reference Example 14, giving the titled product (61 mg) in the form of white solids.

^1H NMR (400 MHz, CDCl_3) δ ppm 7.44 (d, $J = 7.9$ Hz, 1H), 7.26 (t, $J = 8.5$ Hz, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 6.50 (t, $J = 7.6$ Hz, 1H), 5.81 (s, 2H), 3.72 (s, 3H).

MS (ESI+) 423 ($M^+ + 1$, 46%).

Reference Example 26

8-bromo-7-(2-chlorobenzyl)-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



Tert-butyl lithium (1.49 M pentane solution, 29.4 mL) was gradually added at 0°C to a tetrahydrofuran (300 mL) solution of 7-(2-chlorobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one (4.80 g) in a nitrogen atmosphere, and the ingredients were stirred for 2 hours. Then, 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.37 mL) was added at -10°C , and the ingredients were then stirred for 3 hours at 0°C . Saturated sodium bicarbonate aqueous solution was added to the reaction solution, the tetrahydrofuran was distilled off at reduced pressure, and the product was washed with diethyl ether. Dilute hydrochloric acid was added to render the solution acidic before extraction 3 times with chloroform (100 mL). The organic layer was washed with saturated brine, dried over

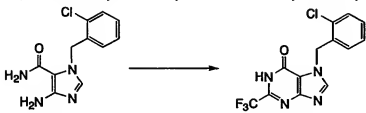
anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The residue was purified by column chromatography (silica gel, chloroform/acetic acid = 100/1 to 25/1), giving the target product (1.11 g).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.55 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.29–7.25 (m, 1H), 6.65 (d, J = 7.7 Hz, 1H), 5.69 (s, 2H), 3.34 (s, 1H).

MS (ESI+) 409 (M^+ +1, 14%).

Reference Example 27

7-(2-chlorobenzyl)-1-methyl-2-trifluoromethyl-1,7-dihydro-6H-purine-6-one



A mixture of 4-amino-1-(2-chlorobenzyl)-5-imidazole carboxamide (5.01 g), trifluoroacetamide (22.6 g), and trifluoroacetic acid (1.54 mL) was stirred for 1 hour at 160°C in a nitrogen atmosphere. After the solution had cooled, diethyl ether (50 mL) was added, the mixture was heated to reflux for 10 minutes and allowed to cool, and the solids were filtered off. Acetonitrile (25 mL) was added to the solids, the material was heated to reflux for 10 minutes and allowed to cool, and the solids were filtered off and dried, giving the titled product (4.97 g) in the form of white solids.

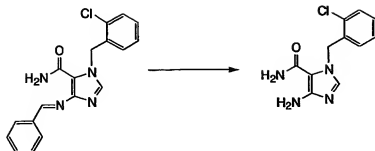
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 13.8 (s, 1H), 8.49 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 5.72 (s, 2H).

MS (ESI+) 329 (M^+ +1, 50%).

Reference Example 28

4-amino-1-(2-chlorobenzyl)-5-imidazole carboxamide

236



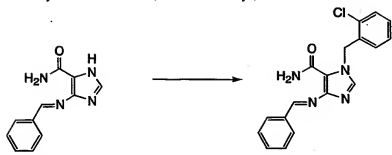
The compound of Reference Example 29 (27.0 g) was used as starting material for synthesis in the same manner as noted in the literature (such as WO 99/03858), giving the titled product (17.0 g) in the form of white solids.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.50 (s, 1H), 7.44 (d, $J = 7.1$ Hz, 1H), 7.30–7.24 (m, 2H), 6.77 (s, 2H), 6.61–6.59 (m, 1H), 5.51 (s, 2H), 5.22 (s, 2H).

MS (ESI+) 251 ($M^+ + 1$, 26%).

Reference Example 29

4-benzylideneamino-1-(2-chlorobenzyl)-5-imidazole carboxamide



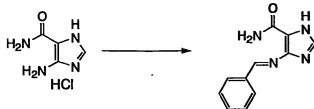
The compound of Reference Example 30 (21.4 g) was used as starting material for synthesis in the same manner as noted in the literature (such as WO 99/03858), giving the titled product (27.4 g) in the form of white solids.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.25 (s, 1H), 8.18 (s, 1H), 8.00 (d, $J = 7.4$ Hz, 1H), 7.95 (s, 1H), 7.60–7.49 (m, 6H), 7.37–7.32 (m, 2H), 6.62 (d, $J = 7.3$ Hz, 1H), 5.74 (s, 2H).

MS (ESI+) 339 ($M^+ + 1$, 55%).

Reference Example 30

4-benzylideneamino-5-imidazole carboxamide

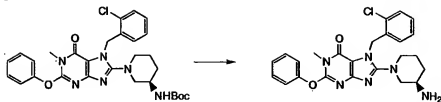


4-aminoimidazole-5-carboxamide hydrochloride (32.6 g) was used as starting material for synthesis in the same manner as noted in the literature (such as WO 99/03858), giving the titled product (39.9 g) in the form of white solids.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.0 (s, 1H), 9.17 (s, 1H), 8.00–7.98 (m, 2H), 7.83 (s, 1H), 7.73 (s, 1H), 7.66 (s, 1H), 7.56–7.51 (m, 3H).

Example 16

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-2-phenoxy-1,7-dihydro-6H-purine-6-one

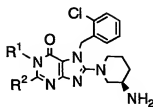


A 4N hydrochloric acid/1,4-dioxane solution (30 mL) was added to a 1,4-dioxane solution (20 mL) solution of tert-butyl[(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate (4.30 g), and the mixture was stirred for 4 hours at 25°C. Saturated sodium bicarbonate aqueous solution (100 mL) was added to the residue, the solution was rendered alkaline, and it was extracted twice with chloroform (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated at reduced pressure, giving the titled product (3.55 g).












¹H NMR (300 MHz, CDCl₃) δ ppm 7.44–7.38 (m, 3H), 7.28–7.16 (m 5H), 6.82 (d, J=7.1Hz, 1H), 5.52–5.50 (m, 2H), 3.63 (s, 3H), 3.39–3.36 (m, 1H), 3.27–3.23 (m, 1H), 2.92–2.85 (m, 2H), 2.69–2.62 (m, 1H), 1.84–1.82 (m, 1H), 1.65–1.55 (m, 2H), 1.23–1.21 (m, 1H)














MS (ESI+) 465 (M⁺+1, 35%) .

Compounds 17 through 61 were synthesized from the compounds of the corresponding reference examples in the same manner as in Example 16.



Example No.	R ¹	R ²	Starting Material Reference Example No.
Example 17	CH ₃		Reference Example 32
Example 18	CH ₃		Reference Example 33
Example 19	CH ₃		Reference Example 34
Example 20	CH ₃		Reference Example 35
Example 21	CH ₃		Reference Example 36
Example 22	CH ₃		Reference Example 37
Example 23	CH ₃		Reference Example 38
Example 24	CH ₃		Reference Example 39
Example 25	CH ₃		Reference Example 40
Example 26	CH ₃ CH ₂ OC(O)CH ₂	PhO	Reference Example 41
Example 27	HOC(O)CH ₂	PhO	Reference Example 42
Example 28		COOH	Reference Example 43
Example 29		CN	Reference Example 44
Example 30	HOC(O)CH ₂	CONH ₂	Reference Example 45
Example 31	CH ₃	PhC(O)	Reference Example 46

Example No.	R ¹	R ²	Starting Material Reference Example No.
Example 32	CH ₃		Reference Example 47
Example 33	CH ₃		Reference Example 48
Example 34	CH ₃	CN	Reference Example 49
Example 35	CH ₃	C(O)CH ₃	Reference Example 50
Example 36	CH ₃	SCH ₃	Reference Example 51
Example 37	CH ₃	S(O) ₂ CH ₃	Reference Example 52
Example 38	CH ₃	S(O) ₂ Ph	Reference Example 53
Example 39	CH ₃	SPh	Reference Example 54
Example 40	CH ₃		Reference Example 55
Example 41	CH ₃		Reference Example 56
Example 42	CH ₃		Reference Example 57
Example 43	CH ₃		Reference Example 58
Example 44	CH ₃		Reference Example 59
Example 45	CH ₃		Reference Example 60
Example 46	CH ₃		Reference Example 61
Example 47	CH ₃		Reference Example 62
Example 48	CH ₃		Reference Example 63

Example No.	R ¹	R ²	Starting Material Reference Example No.
Example 49	CH ₃		Reference Example 64
Example 50	CH ₃		Reference Example 65
Example 51	CH ₃		Reference Example 66
Example 52	CH ₃		Reference Example 80
Example 53	CH ₃		Reference Example 81
Example 54	CH ₃		Reference Example 82
Example 55	CH ₃		Reference Example 83
Example 56	CH ₃		Reference Example 84
Example 57	CH ₃		Reference Example 85
Example 58	CH ₃		Reference Example 86
Example 59	CH ₃		Reference Example 87
Example 60	CH ₃		Reference Example 88
Example 61	CH ₃		Reference Example 89

Example 17

^1H NMR (300MHz, CDCl_3) δ ppm 7.42-7.39 (m, 1H), 7.22-7.16 (m, 2H), 6.83-6.74 (m, 3H), 6.65 (dd, $J=2.4, 8.2$ Hz, 1H), 6.00 (s, 2H), 5.51-5.50 (m, 2H), 3.60 (s, 3H), 3.39-3.24 (m, 1H), 3.28-3.24 (m, 1H), 2.92-2.85 (m, 2H), 2.69-2.62 (m, 1H), 1.84-1.82 (m, 1H), 1.65-1.52 (m, 2H), 1.25-1.19 (m, 1H).
MS (ESI+) 509 ($M^+ + 1$, 34%).

Example 18

^1H NMR (300MHz, CDCl_3) δ ppm 8.56-8.51 (m, 2H), 7.68-7.65 (m, 1H), 7.43-7.36 (m, 2H), 7.23-7.19 (m, 2H), 6.84-6.81 (m, 1H), 5.52-5.51 (m, 2H), 3.65 (s, 3H), 3.40-3.36 (m, 1H), 3.26-3.24 (m, 1H), 3.89-3.86 (m, 2H), 2.70-2.63 (m, 1H), 1.85-1.83 (m, 1H), 1.60-1.58 (m, 2H), 1.25-1.18 (m, 1H).
MS (ESI+) 466 ($M^+ + 1$, 11%).

Example 19

^1H NMR (300MHz, CDCl_3) δ ppm 7.42-7.34 (m, 3H), 7.23-7.01 (m, 9H), 6.82 (d, $J=7.1$ Hz, 1H), 5.52-5.51 (m, 2H), 3.62 (s, 3H), 3.40-3.37 (m, 1H), 3.26-3.24 (m, 1H), 2.93-2.87 (m, 2H), 2.69-2.63 (m, 1H), 1.86-1.84 (m, 1H), 1.66-1.58 (m, 2H), 1.21-1.18 (m, 1H).
MS (ESI+) 557 ($M^+ + 1$, 20%).

Example 20

^1H NMR (400MHz, CDCl_3) δ ppm 7.42-7.36 (m, 3H), 7.20-7.17 (m, 4H), 6.87-6.82 (m, 1H), 5.55-5.50 (m, 2H), 3.62 (s, 3H), 3.42-3.37 (m, 1H), 3.32-3.27 (m, 1H), 2.93-2.88 (m, 2H), 2.65 (dd, $J=8.8, 12.2$ Hz, 1H), 1.72-1.66 (m, 1H), 1.64-1.51 (m, 2H), 1.26-1.21 (m, 1H).
MS (ESI+) 499 ($M^+ + 1$, 100%).

Example 21

^1H NMR (400MHz, CDCl_3) δ ppm 7.42-7.40 (m, 1H), 7.27-7.20 (m, 4H), 7.12-7.09 (m, 2H), 6.80 (d, $J=7.4$ Hz, 1H), 5.57-5.50 (m, 2H), 3.62 (s, 3H), 3.42-3.37 (m, 1H), 3.30-3.25 (m, 1H), 2.93-2.88 (m, 2H), 2.65 (dd, $J=8.8, 12.2$ Hz, 1H), 1.90-1.85 (m, 1H), 1.71-1.66 (m, 2H), 1.26-1.21 (m, 1H).

MS (ESI+) 483 ($M^+ + 1$, 100%).

Example 22

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.23–7.13 (m, 6H), 6.86–6.83 (m, 1H), 5.51–5.50 (m, 2H), 3.65 (s, 3H), 3.38–3.35 (m, 1H), 3.27–3.23 (m, 1H), 2.91–2.84 (m, 2H), 2.68–2.61 (m, 1H), 2.21 (s, 3H), 1.85–1.83 (m, 1H), 1.66–1.52 (m, 2H), 1.22–1.20 (m, 1H).

MS (ESI+) 479 ($M^+ + 1$, 29%).

Example 23

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.31–7.16 (m, 3H), 7.07–7.00 (m, 3H), 6.82 (d, $J=7.1\text{Hz}$, 1H), 5.52–5.50 (m, 2H), 3.61 (s, 3H), 3.39–3.34 (m, 1H), 3.27–3.23 (m, 1H), 2.92–2.84 (m, 2H), 2.69–2.62 (m, 1H), 2.37 (s, 3H), 1.84–1.82 (m, 1H), 1.65–1.57 (m, 2H), 1.22–1.18 (m, 1H).

MS (ESI+) 479 ($M^+ + 1$, 30%).

Example 24

^1H NMR (300MHz, CDCl_3) δ ppm 7.43–7.40 (m, 1H), 7.27–7.16 (m, 6H), 6.82 (d, $J=7.3\text{Hz}$, 1H), 5.55 (d, $J=17.4\text{Hz}$, 1H), 5.48 (d, $J=17.4\text{Hz}$, 1H), 3.62 (s, 3H), 3.40–3.36 (m, 1H), 3.29–3.25 (m, 1H), 2.94–2.84 (m, 2H), 2.69–2.62 (m, 1H), 2.36 (s, 3H), 1.85–1.83 (m, 1H), 1.68–1.53 (m, 2H), 1.26–1.18 (m, 1H).

MS (ESI+) 549 ($M^+ + 1$, 33%).

Example 25

^1H NMR (300MHz, CDCl_3) δ ppm 7.44–7.35 (m, 2H), 7.25–7.19 (m, 2H), 7.11–7.09 (m, 2H), 7.04–7.00 (m, 1H), 6.90–6.88 (m, 1H), 5.60–5.59 (m, 2H), 3.85 (s, 3H), 3.49–3.47 (m, 1H), 3.48 (s, 3H), 3.35–3.33 (m, 1H), 3.00–2.91 (m, 2H), 2.76–2.69 (m, 1H), 1.90–1.88 (m, 1H), 1.69–1.63 (m, 2H), 1.27–1.25 (m, 1H).

MS (ESI+) 479 ($M^+ + 1$, 31%).

Example 26

^1H NMR (400MHz, $\text{DMSO}-d_6$) δ ppm 7.44–7.39 (m, 3H), 7.26–7.21 (m, 3H), 7.14–7.09 (m, 2H), 6.70–6.65 (m, 1H), 5.31 (s, 2H), 4.79 (s, 2H), 4.06 (q, $J=7.1$

Hz, 2H), 3.23-3.17 (m, 1H), 3.70-3.65 (m, 1H), 2.31-2.56 (m, 1H), 2.40-2.22 (m, 2H), 1.68-1.63 (m, 1H), 1.50-1.45 (m, 1H), 1.33-1.28 (m, 2H), 1.08 (t, J=7.1 Hz, 3H).

MS (ESI+) 537 ($M^+ + 1$, 100%).

Example 27

^1H NMR (400MHz, DMSO- d_6) δ ppm 7.57-7.52 (m, 3H), 7.41-7.36 (m, 3H), 7.26-7.21 (m, 2H), 6.88-6.82 (m, 1H), 5.46 (s, 2H), 4.82 (s, 2H), 3.59-3.54 (m, 1H), 3.18-3.13 (m, 1H), 3.14-3.09 (m, 2H), 2.92-2.87 (m, 1H), 1.97-1.92 (m, 1H), 1.77-1.72 (m, 1H), 1.55-1.50 (m, 2H).

MS (ESI+) 509 ($M^+ + 1$, 100%).

Example 28

^1H NMR (400MHz, DMSO- d_6) δ ppm 7.51 (d, J=7.7Hz, 1H), 7.36-7.25 (m, 2H), 6.87-6.81 (m, 1H), 5.53 (s, 2H), 3.68-3.66 (m, 1H), 3.31-3.29 (m, 1H), 3.18-3.11 (m, 2H), 2.85-2.83 (m, 1H), 1.95-1.93 (m, 1H), 1.73-1.71 (m, 1H), 1.56-1.52 (m, 2H).

MS (ESI+) 403 ($M^+ + 1$, 100%).

Example 29

^1H NMR (400MHz, CD $_3$ OD) δ ppm 8.29-8.24 (m, 1H), 7.89-7.84 (m, 2H), 7.60-7.55 (m, 1H), 7.55-7.50 (m, 1H), 7.35 (d, J=7.8Hz, 1H), 7.22-7.17 (m, 2H), 8.0 (d, J=8.0Hz, 1H), 5.52 (s, 2H), 5.12 (s, 2H), 3.71-3.66 (m, 1H), 3.43-3.38 (m, 2H), 3.20-3.15 (m, 1H), 2.95-2.90 (m, 1H), 2.05-2.00 (m, 1H), 1.73-1.68 (m, 1H), 1.57-1.52 (m, 2H).

MS (ESI+) 518 ($M^+ + 1$, 100%).

Example 30

^1H NMR (400MHz, CD $_3$ OD) δ ppm 7.42-7.37 (m, 1H), 7.25-7.20 (m, 2H), 6.90-6.85 (m, 1H), 5.54 (s, 2H), 5.10 (s, 2H), 3.70-3.65 (m, 1H), 3.42-3.37 (m, 1H), 3.20-3.15 (m, 2H), 2.98-2.93 (m, 1H), 2.05-2.00 (m, 1H), 1.77-1.72 (m, 1H), 1.62-1.57 (m, 2H).

MS (ESI+) 460 ($M^+ + 1$, 100%).

Example 31

¹H NMR(300MHz, CDCl₃) δ ppm 8.03-8.01 (m, 2H), 7.69-7.64 (m, 1H), 7.53-7.38 (m, 3H), 7.26-7.21 (m, 2H), 6.89-6.87 (m, 1H), 5.60-5.59 (m, 2H), 3.56-3.54 (m, 1H), 3.52 (s, 3H), 3.32-3.30 (m, 1H), 2.99-2.95 (m, 2H), 2.83-2.76 (m, 1H), 1.93-1.91 (m, 1H), 1.67-1.60 (m, 2H), 1.27-1.25 (m, 1H).

MS (ESI+) 477 (M⁺+1, 100%) .

Example 32

¹H NMR(300MHz, CDCl₃) δ ppm 8.63 (s, 1H), 8.05-7.96 (m, 4H), 7.74-7.64 (m, 2H), 7.42-7.39 (m, 1H), 7.24-7.18 (m, 2H), 6.72 (d, J=7.5Hz, 1H), 5.54-5.53 (m, 2H), 4.07 (s, 3H), 3.29-3.27 (m, 1H), 3.16-3.14 (m, 1H), 2.83-2.81 (m, 2H), 2.66-2.59 (m, 1H), 1.85-1.83 (m, 1H), 1.62-1.49 (m, 2H), 1.20-1.18 (m, 1H).

MS (ESI+) 563 (M⁺+1, 100%) .

Example 33

¹H NMR(300MHz, CDCl₃) δ ppm 8.13 (s, 1H), 7.92-7.83 (m, 3H), 7.67-7.64 (m, 1H), 7.59-7.50 (m, 2H), 7.41-7.38 (m, 1H), 7.24-7.14 (m, 2H), 6.76 (d, J=7.4Hz, 1H), 5.51-5.50 (m, 2H), 3.69 (s, 3H), 3.31-3.28 (m, 1H), 3.20-3.16 (m, 1H), 2.86-2.82 (m, 2H), 2.63-2.56 (m, 1H), 1.79-1.77 (m, 1H), 1.61-1.48 (m, 2H), 1.17-1.15 (m, 1H).

MS (ESI+) 531 (M⁺+1, 37%) .

Example 34

¹H NMR(300MHz, CDCl₃) δ ppm 7.45-7.42 (m, 1H), 7.29-7.18 (m, 2H), 6.77 (d, J=6.1Hz, 1H), 5.57 (s, 2H), 3.78 (s, 3H), 3.53-3.48 (m, 1H), 3.42-3.38 (m, 1H), 3.03-2.89 (m, 2H), 2.78-2.71 (m, 1H), 1.90-1.88 (m, 1H), 1.71-1.60 (m, 2H), 1.26-1.24 (m, 1H).

MS (ESI+) 398 (M⁺+1, 100%) .

Example 35

¹H NMR(300MHz, CDCl₃) δ ppm 7.42 (d, J=7.5Hz, 1H), 7.24-7.17 (m, 2H), 6.80 (d, J=7.4Hz, 1H), 5.60-5.59 (m, 2H), 3.70 (s, 3H), 3.50-3.46 (m, 1H), 3.39-3.35 (m, 1H), 3.01-2.93 (m, 2H), 2.77 (s, 3H), 2.76-2.74 (m, 1H), 1.90-1.88 (m, 1H), 1.71-1.63 (m, 2H), 1.26-1.24 (m, 1H).

MS (ESI+) 415 ($M^+ + 1$, 100%) .

Example 36

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.24–7.15 (m, 2H), 6.81 (d, $J=7.1\text{Hz}$, 1H), 5.53–5.51 (m, 2H), 3.53 (s, 3H), 3.45–3.40 (m, 1H), 3.33–3.29 (m, 1H), 2.97–2.88 (m, 2H), 2.74–2.70 (m, 1H), 2.68 (s, 3H), 1.87–1.85 (m, 1H), 1.69–1.61 (m, 2H), 1.26–1.24 (m, 1H).

MS (ESI+) 415 ($M^+ + 1$, 100%) .

Example 37

^1H NMR (300MHz, CDCl_3) δ ppm 7.45–7.42 (m, 1H), 7.27–7.19 (m, 2H), 6.79 (d, $J=7.3\text{Hz}$, 1H), 5.59–5.58 (m, 2H), 3.89 (s, 3H), 3.56 (s, 3H), 3.49–3.45 (m, 1H), 3.39–3.35 (m, 1H), 3.01–2.94 (m, 2H), 2.78–2.71 (m, 1H), 1.89–1.91 (m, 1H), 1.73–1.63 (m, 2H), 1.26–1.24 (m, 1H).

MS (ESI+) 451 ($M^+ + 1$, 100%) .

Example 38

^1H NMR (300MHz, CDCl_3) δ ppm 8.07–8.04 (m, 2H), 7.77–7.72 (m, 1H), 7.65–7.60 (m, 2H), 7.43–7.40 (m, 1H), 7.24–7.18 (m, 2H), 6.73 (d, $J=7.3\text{Hz}$, 1H), 5.56–5.55 (m, 2H), 4.04 (s, 3H), 3.34–3.32 (m, 1H), 3.22–3.20 (m, 1H), 2.88–2.86 (m, 2H), 2.67–2.61 (m, 1H), 1.88–1.86 (m, 1H), 1.71–1.55 (m, 2H), 1.26–1.24 (m, 1H).

MS (ESI+) 513 ($M^+ + 1$, 100%) .

Example 39

^1H NMR (300MHz, CDCl_3) δ ppm 7.64–7.61 (m, 2H), 7.46–7.38 (m, 4H), 7.23–7.13 (m, 2H), 6.75 (d, $J=7.3\text{Hz}$, 1H), 5.51–5.50 (m, 2H), 3.65 (s, 3H), 3.35–3.31 (m, 1H), 3.23–3.19 (m, 1H), 2.89–2.83 (m, 2H), 2.66–2.59 (m, 1H), 1.82–1.80 (m, 1H), 1.64–1.55 (m, 2H), 1.20–1.18 (m, 1H).

MS (ESI+) 481 ($M^+ + 1$, 25%) .

Example 40

^1H NMR (300MHz, CDCl_3) δ ppm 7.44–7.41 (m, 1H), 7.25–7.19 (m, 2H), 7.10–7.09 (m, 2H), 6.88–6.86 (m, 1H), 6.36–6.34 (m, 2H), 5.56 (s, 2H), 3.50 (s, 3H), 3.42–3.34 (m, 2H), 2.97–2.94 (m, 2H), 2.79–2.72 (m, 1H), 1.82–1.62 (m,

3H), 1.26-1.21 (m, 1H).

MS (ESI+) 438 ($M^+ + 1$, 100%).

Example 41

^1H NMR (300MHz, CDCl_3) δ ppm 7.42-7.39 (m, 1H), 7.24-7.19 (m, 2H), 6.87-6.85 (m, 1H), 5.54 (s, 2H), 3.68-3.62 (m, 2H), 3.53 (s, 3H), 3.46-3.43 (m, 1H), 3.31-3.30 (m, 1H), 2.94-2.91 (m, 2H), 2.73-2.69 (m, 1H), 2.61-2.56 (m, 2H), 2.27-2.23 (m, 2H), 1.87-1.85 (m, 1H), 1.68-1.58 (m, 2H), 1.26-1.24 (m, 1H).

MS (ESI+) 456 ($M^+ + 1$, 100%).

Example 42

^1H NMR (300MHz, CDCl_3) δ ppm 7.97-7.93 (m, 1H), 7.88-7.87 (m, 1H), 7.53-7.39 (m, 3H), 7.24-7.17 (m, 2H), 6.83 (d, $J=7.0\text{Hz}$, 1H), 5.55 (d, $J=17.1\text{Hz}$, 1H), 5.48 (d, $J=17.1\text{Hz}$, 1H), 3.92 (s, 3H), 3.64 (s, 3H), 3.39-3.34 (m, 1H), 3.24-3.22 (m, 1H), 2.91-2.85 (m, 2H), 2.70-2.62 (m, 1H), 1.84-1.82 (m, 1H), 1.60-1.56 (m, 2H), 1.23-1.21 (m, 1H).

MS (ESI+) 523 ($M^+ + 1$, 29%).

Example 43

^1H NMR (300MHz, $\text{DMSO}-d_6$) δ ppm 7.92-7.85 (m, 2H), 7.66-7.51 (m, 3H), 7.35-7.26 (m, 2H), 6.79 (d, $J=6.1\text{Hz}$, 1H), 5.46 (s, 2H), 3.57 (s, 3H), 3.46-3.27 (m, 2H), 3.11-3.04 (m, 2H), 2.89-2.79 (m, 1H), 1.92-1.90 (m, 1H), 1.69-1.45 (m, 3H).

MS (ESI+) 509 ($M^+ + 1$, 56%).

Example 44

^1H NMR (300MHz, CDCl_3) δ ppm 7.97-7.95 (m, 1H), 7.86 (d, $J=2.2\text{Hz}$, 1H), 7.52-7.40 (m, 3H), 7.24-7.17 (m, 2H), 6.83 (d, $J=7.1\text{Hz}$, 1H), 5.52-5.51 (m, 2H), 4.39 (dd, $J=7.1, 14.3\text{Hz}$, 2H), 3.64 (s, 3H), 3.39-3.35 (m, 1H), 3.25-3.23 (m, 1H), 2.92-2.84 (m, 2H), 2.68-2.61 (m, 1H), 1.85-1.83 (m, 1H), 1.65-1.57 (m, 2H), 1.40 (t, $J=7.1\text{Hz}$, 3H), 1.22-1.20 (m, 1H).

MS (ESI+) 537 ($M^+ + 1$, 23%).

Example 45

^1H NMR (300MHz, CDCl_3) δ ppm 7.46–7.40 (m, 2H), 7.24–7.13 (m, 5H), 6.83 (d, $J=7.3\text{Hz}$, 1H), 5.52–5.51 (m, 2H), 3.62 (s, 3H), 3.40–3.36 (m, 1H), 3.30–3.25 (m, 1H), 2.93–2.86 (m, 2H), 2.69–2.62 (m, 1H), 1.85–1.83 (m, 1H), 1.66–1.58 (m, 2H), 1.23–1.20 (m, 1H).

MS (ESI+) 549 ($M^+ + 1$, 33%).

Example 46

^1H NMR (300MHz, CDCl_3) δ ppm 7.43–7.18 (m, 7H), 6.87–6.84 (m, 1H), 5.54 (d, $J=17.0\text{Hz}$, 1H), 5.48 (d, $J=17.0\text{Hz}$, 1H), 3.64 (s, 3H), 3.39–3.35 (m, 1H), 3.28–3.24 (m, 1H), 2.91–2.84 (m, 2H), 2.68–2.61 (m, 1H), 1.85–1.83 (m, 1H), 1.65–1.57 (m, 2H), 1.25–1.20 (m, 1H).

MS (ESI+) 549 ($M^+ + 1$, 31%).

Example 47

^1H NMR (300MHz, CDCl_3) δ ppm 7.59–7.51 (m, 4H), 7.43–7.40 (m, 1H), 7.24–7.17 (m, 2H), 6.82 (d, $J=7.1\text{Hz}$, 1H), 5.55 (d, $J=17.6\text{Hz}$, 1H), 5.48 (d, $J=17.6\text{Hz}$, 1H), 3.63 (s, 3H), 3.40–3.37 (m, 1H), 3.30–3.25 (m, 1H), 2.93–2.86 (m, 2H), 2.71–2.63 (m, 1H), 1.84–1.52 (m, 3H), 1.23–1.19 (m, 1H).

MS (ESI+) 490 ($M^+ + 1$, 54%).

Example 48

^1H NMR (300MHz, CDCl_3) δ ppm 7.43–7.33 (m, 2H), 7.24–7.16 (m, 1H), 7.05–6.96 (m, 3H), 6.83–6.80 (m, 2H), 5.55 (d, $J=17.4\text{Hz}$, 1H), 5.48 (d, $J=17.4\text{Hz}$, 1H), 3.62 (s, 3H), 3.40–3.37 (m, 1H), 3.29–3.25 (m, 1H), 2.94–2.85 (m, 2H), 2.69–2.63 (m, 1H), 1.86–1.84 (m, 1H), 1.67–1.55 (m, 2H), 1.25–1.18 (m, 1H).

MS (ESI+) 483 ($M^+ + 1$, 85%).

Example 49

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.32–7.16 (m, 3H), 6.84–6.75 (m, 4H), 5.54 (d, $J=17.2\text{Hz}$, 1H), 5.48 (d, $J=17.2\text{Hz}$, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.39–3.35 (m, 1H), 3.28–3.23 (m, 1H), 2.92–2.84 (m, 2H), 2.69–2.62 (m, 1H), 1.84–1.82 (m, 1H), 1.65–1.58 (m, 2H), 1.22–1.20 (m, 1H).

MS (ESI+) 495 ($M^+ + 1$, 57%).

Example 50

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.23–7.16 (m, 2H), 6.85–6.81 (m, 1H), 6.38 (s, 2H), 6.37 (s, 1H), 5.54 (d, $J=17.1\text{Hz}$, 1H), 5.48 (d, $J=17.1\text{Hz}$, 1H), 3.78 (s, 6H), 3.60 (s, 3H), 3.40–3.36 (m, 1H), 3.29–3.24 (m, 1H), 2.93–2.84 (m, 2H), 2.69–2.62 (m, 1H), 1.84–1.82 (m, 1H), 1.67–1.58 (m, 2H), 1.26–1.18 (m, 1H).

MS (ESI+) 525 ($\text{M}^+ + 1$, 59%) .

Example 51

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.31–7.16 (m, 3H), 6.84–6.71 (m, 4H), 5.54 (d, $J=17.4\text{Hz}$, 1H), 5.48 (d, $J=17.4\text{Hz}$, 1H), 3.87–3.83 (m, 4H), 3.61 (s, 3H), 3.39–3.36 (m, 1H), 3.28–3.24 (m, 1H), 3.19–3.16 (m, 4H), 2.92–2.84 (m, 2H), 2.68–2.61 (m, 1H), 1.84–1.82 (m, 1H), 1.65–1.52 (m, 2H), 1.21–1.18 (m, 1H).

MS (ESI+) 550 ($\text{M}^+ + 1$, 26%) .

Example 52

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.38 (m, 1H), 7.23–7.18 (m, 4H), 6.99–6.94 (m, 2H), 6.84–6.83 (m, 1H), 5.54 (d, $J=18.1\text{Hz}$, 1H), 5.47 (d, $J=18.1\text{Hz}$, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 3.38–3.34 (m, 1H), 3.26–3.22 (m, 1H), 2.90–2.83 (m, 2H), 2.67–2.60 (m, 1H), 1.85–1.82 (m, 1H), 1.65–1.52 (m, 2H), 1.25–1.18 (m, 1H).

MS (ESI+) 495 ($\text{M}^+ + 1$, 100%) .

Example 53

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.38 (m, 1H), 7.23–7.12 (m, 4H), 6.93–6.89 (m, 2H), 6.83–6.80 (m, 1H), 5.54 (d, $J=17.4\text{Hz}$, 1H), 5.47 (d, $J=17.4\text{Hz}$, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 3.38–3.34 (m, 1H), 3.25–3.21 (m, 1H), 2.91–2.84 (m, 2H), 2.68–2.61 (m, 1H), 1.85–1.82 (m, 1H), 1.65–1.44 (m, 2H), 1.26–1.21 (m, 1H).

MS (ESI+) 495 ($\text{M}^+ + 1$, 100%) .

Example 54

^1H NMR (400MHz, CDCl_3) δ ppm 7.54–7.50 (m, 2H), 7.48–7.47 (m, 2H), 7.41 (dd,

$J=1.5$, 7.8Hz, 1H), 7.28-7.18 (m, 2H), 6.82 (dd, $J=1.3$, 7.3Hz, 1H), 5.51 (m, 2H), 3.64 (s, 3H), 3.41-3.37 (m, 1H), 3.27-3.24 (m, 1H), 2.91-2.85 (m, 2H), 2.66 (dd, $J=9.0$, 12.1Hz, 1H), 1.68-1.53 (m, 3H), 1.22-1.19 (m, 1H).
MS (ESI+) 533 (M^+1 , 100%).

Example 55

^1H NMR (400MHz, CDCl_3) δ ppm 7.42-7.40 (m, 1H), 7.26-7.18 (m, 2H), 6.88-6.74 (m, 4H), 5.51-5.50 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.62 (s, 3H), 3.39-3.36 (m, 1H), 3.27-3.24 (m, 1H), 2.91-2.85 (m, 2H), 2.68-2.63 (m, 1H), 1.88-1.84 (m, 1H), 1.68-1.56 (m, 2H), 1.21-1.19 (m, 1H).
MS (ESI+) 525 (M^+1 , 100%).

Example 56

^1H NMR (400MHz, CDCl_3) δ ppm 7.37 (dd, $J=1.6$, 7.8Hz, 1H), 7.27-7.16 (m, 3H), 6.81-6.77 (m, 4H), 5.52-5.42 (m, 2H), 4.11-4.09 (m, 2H), 3.74-3.71 (m, 2H), 3.58 (s, 3H), 3.43 (s, 3H), 3.45-3.38 (m, 1H), 3.25-3.15 (m, 1H), 2.87-2.84 (m, 2H), 2.68-2.63 (m, 1H), 1.86-1.82 (m, 1H), 1.63-1.58 (m, 1H), 1.58-1.51 (m, 1H), 1.22-1.18 (m, 1H).
MS (ESI+) 539 (M^+1 , 100%).

Example 57

^1H NMR (400MHz, CDCl_3) δ ppm 8.06 (dd, $J=1.6$, 7.8Hz, 1H), 7.61-7.60 (m, 1H), 7.40 (dd, $J=1.7$, 7.7Hz, 1H), 7.36-7.32 (m, 1H), 7.23-7.19 (m, 3H), 6.84 (dd, $J=1.6$, 7.2Hz, 1H), 5.55-5.45 (m, 2H), 3.76 (s, 3H), 3.64 (s, 3H), 3.38-3.50 (m, 1H), 3.23-3.20 (m, 1H), 2.89-2.82 (m, 2H), 2.68-2.63 (m, 1H), 1.87-1.82 (m, 1H), 1.63-1.56 (m, 2H), 1.25-1.18 (m, 1H).
MS (ESI+) 523 (M^+1 , 100%).

Example 58

^1H NMR (400MHz, CDCl_3) δ ppm 8.12-8.09 (m, 2H), 7.41 (dd, $J=1.5$, 7.8Hz, 1H), 7.33-7.31 (m, 2H), 7.24-7.19 (m, 2H), 6.83-6.82 (m, 1H), 5.55-5.46 (m, 2H), 3.94 (s, 3H), 3.63 (s, 3H), 3.40-3.37 (m, 1H), 3.28-3.25 (m, 1H), 2.91-2.85 (m, 2H), 2.69-2.63 (m, 1H), 2.27-1.85 (m, 1H), 1.67-1.43 (m, 2H), 1.21-1.19 (m, 1H).

MS (ESI+) 523 ($M^+ + 1$, 100%) .

Example 59

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.23–7.16 (m, 2H), 6.87–6.81 (m, 2H), 6.76–6.66 (m, 2H), 5.51–5.49 (m, 2H), 4.26 (s, 4H), 3.67–3.36 (m, 1H), 3.59 (s, 3H), 3.39–3.35 (m, 1H), 3.28–3.23 (m, 1H), 2.92–2.88 (m, 2H), 2.68–2.61 (m, 1H), 1.85–1.82 (m, 1H), 1.65–1.45 (m, 2H), 1.26–1.21 (m, 1H).

MS (ESI+) 523 ($M^+ + 1$, 11%) .

Example 60

^1H NMR (300MHz, CDCl_3) δ ppm 7.43–7.40 (m, 1H), 7.27–7.16 (m, 6H), 6.82 (d, $J=7.3\text{Hz}$, 1H), 5.55 (d, $J=17.0\text{Hz}$, 1H), 5.48 (d, $J=17.0\text{Hz}$, 1H), 3.26 (s, 3H), 3.40–3.36 (m, 1H), 3.29–3.25 (m, 1H), 2.94–2.84 (m, 2H), 2.69–2.62 (m, 1H), 1.85–1.83 (m, 1H), 1.68–1.53 (m, 2H), 1.26–1.18 (m, 1H).

MS (ESI+) 549 ($M^+ + 1$, 33%) .

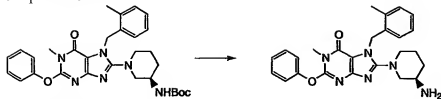
Example 61

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.39 (m, 1H), 7.31–7.16 (m, 3H), 6.84–6.74 (m, 4H), 5.57–5.44 (m, 2H), 4.03 (dd, $J=6.9, 13.9\text{Hz}$, 2H), 3.61 (s, 3H), 3.39–3.35 (m, 1H), 3.23–3.21 (m, 1H), 2.92–2.89 (m, 2H), 2.71–2.64 (m, 1H), 1.84–1.81 (m, 1H), 1.67–1.57 (m, 2H), 1.41 (t, $J=6.9\text{Hz}$, 3H), 1.26–1.24 (m, 1H).

MS (ESI+) 509 ($M^+ + 1$, 12%) .

Example 62

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-methylbenzyl)-1-methyl-2-phenoxy-1,7-dihydro-6H-purine-6-one



Compound 62 was synthesized from the compound of the corresponding reference

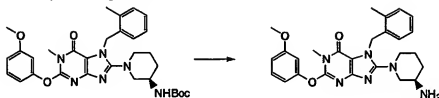
example in the same manner as in Example 16.

¹H NMR (300MHz, CDCl₃) δ ppm 7.40 (t, J=7.9Hz, 2H), 7.27-7.08 (m, 6H), 6.70 (d, J=7.5Hz, 1H), 5.44 (d, J=16.3Hz, 1H), 5.35 (d, J=16.3Hz, 1H), 3.61 (s, 3H), 3.39-3.36 (m, 1H), 3.29-3.24 (m, 1H), 2.92-2.82 (m, 2H), 2.71-2.63 (m, 1H), 2.37 (s, 3H), 1.85-1.81 (m, 1H), 1.65-1.53 (m, 2H), 1.27-1.21 (m, 1H).

MS (ESI+) 445 (M⁺+1, 18%).

Example 63

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-methylbenzyl)-1-methyl-2-(3-methoxyphenoxy)-1,7-dihydro-6H-purine-6-one



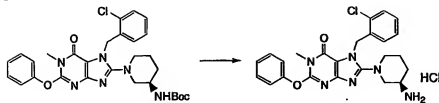
Compound 63 was synthesized from the compound of the corresponding reference example in the same manner as in Example 16.

¹H NMR (300MHz, CDCl₃) δ ppm 7.32-7.12 (m, 4H), 6.83-6.69 (m, 4H), 5.41-5.32 (m, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 3.40-3.29 (m, 2H), 2.93-2.86 (m, 2H), 2.71-2.64 (m, 1H), 2.37 (s, 3H), 1.88-1.85 (m, 1H), 1.65-1.43 (m, 2H), 1.26-1.21 (m, 1H).

MS (ESI+) 475 (M⁺+1, 14%).

Example 64

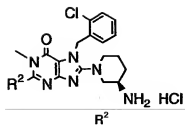
8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-2-phenoxy-1,7-dihydro-6H-purine-6-one




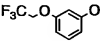
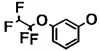
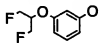

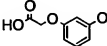
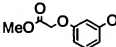
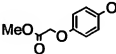


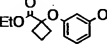

Hydrochloric acid (2N, 0.80 mL) was added at room temperature to a 2-propanol solution (9.5 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (0.75 g), and the mixture was stirred for 30 minutes at 85°C. The reaction solution was gradually cooled to room temperature, and the crystals were filtered off and dried, giving the titled compound (625 mg) in the form of white crystals.



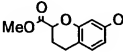


¹H NMR (400MHz, DMSO-d₆) δ ppm 8.05-7.95 (br, 3H), 7.53-7.47 (m, 3H), 7.35-7.26 (m, 5H), 6.76 (d, J=6.3Hz, 1H), 5.43 (s, 2H), 3.52-3.49 (m, 1H), 3.48 (s, 3H), 3.39-3.32 (m, 1H), 3.05-3.00 (m, 2H), 2.83-2.79 (m, 1H), 1.91-1.88 (m, 1H), 1.67-1.51 (m, 1H), 1.47-1.44 (m, 2H).
MS (ESI+) 465 (M⁺+1, 100%) .

Compounds 65 through 94 were synthesized from the compounds of the corresponding reference examples in the same manner as in Example 64.



Example No.	R^2	Starting Material Reference Example No.
Example 65		Reference Example 64
Example 66		Reference Example 90
Example 67		Reference Example 89
Example 68		Reference Example 91
Example 69		Reference Example 92
Example 70		Reference Example 93
Example 71		Reference Example 94
Example 72		Reference Example 95
Example 73		Reference Example 96
Example 74		Reference Example 97
Example 75		Reference Example 32
Example 76		Reference Example 98
Example 77		Reference Example 60

Example No.	R ²	Starting Material Reference Example No.
Example 78		Reference Example 99
Example 79		Reference Example 100
Example 80		Reference Example 101
Example 81		Reference Example 102
Example 82		Reference Example 103
Example 83		Reference Example 104
Example 84		Reference Example 105
Example 85		Reference Example 106
Example 86		Reference Example 107
Example 87		Reference Example 108
Example 88		Reference Example 109
Example 89		Reference Example 110

Example No.	R ²	Starting Material Reference Example No.
Example 90		Reference Example 57
Example 91		Reference Example 111
Example 92		Reference Example 112
Example 93		Reference Example 132
Example 94		Reference Example 127

Example 65

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.34 (br, 3H), 7.53-7.51 (m, 1H), 7.41-7.28 (m, 3H), 6.93-6.87 (m, 4H), 5.48 (d, J=17.4Hz, 1H), 5.43 (d, J=17.4Hz, 1H), 3.78 (s, 3H), 3.57-3.54 (m, 1H), 3.46 (s, 3H), 3.32-3.24 (m, 1H), 3.13-3.04 (m, 2H), 2.85-2.76 (m, 1H), 1.97-1.90 (m, 1H), 1.72-1.64 (m, 1H), 1.58-1.52 (m, 1H), 1.48-1.40 (m, 1H).

MS (ESI+) 495 (M⁺+1, 57%).

Example 66

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.34 (br, 3H), 7.52 (d, J=7.7Hz, 1H), 7.36-7.22 (m, 3H), 6.85 (d, J=7.1Hz, 1H), 6.76-6.69 (m, 3H), 5.48 (d, J=18.1Hz, 1H), 5.42 (d, J=18.1Hz, 1H), 3.59-3.55 (m, 1H), 3.45 (s, 3H), 3.30-3.28 (m, 1H), 3.16-3.05 (m, 2H), 2.85-2.83 (m, 1H), 1.92-1.90 (m, 1H), 1.70-1.68 (m, 1H), 1.56-1.47 (m, 3H).

MS (ESI+) 481 (M⁺+1, 100%).

Example 67

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.19 (br, 3H), 7.52 (t, J=7.5Hz, 1H), 7.40-

7.25 (m, 3H), 6.91-6.78 (m, 4H), 5.45 (s, 2H), 4.05 (dd, J=6.8, 13.8Hz, 2H), 3.60-3.59 (m, 1H), 3.44 (s, 3H), 3.32-3.30 (m, 1H), 3.10-3.03 (m, 2H), 2.85-2.78 (m, 1H), 1.92-1.90 (m, 1H), 1.70-1.67 (m, 1H), 1.55-1.46 (m, 2H), 1.34 (t, J=6.8Hz, 3H).

MS (ESI+) 509 (M^+1 , 12%) .

Example 68

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.19 (br, 3H), 7.52-7.48 (m, 1H), 7.37-7.24 (m, 3H), 6.88-6.76 (m, 4H), 5.43 (s, 2H), 4.66-4.57 (m, 1H), 3.54-3.52 (m, 1H), 3.45 (s, 3H); 3.28-3.26 (m, 1H), 3.09-3.01 (m, 2H), 2.80-2.78 (m, 1H), 1.90-1.88 (m, 1H), 1.68-1.66 (m, 1H), 1.51-1.47 (m, 2H), 1.27 (d, J=6.0Hz, 6H).

MS (ESI+) 523 (M^+1 , 100%) .

Example 69

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.29 (br, 3H), 7.51-7.48 (m, 1H), 7.38-7.26 (m, 3H), 6.90-6.78 (m, 4H), 5.46 (d, J=18.3Hz, 1H), 5.40 (d, J=18.3Hz, 1H), 3.93 (t, J=6.5Hz, 2H), 3.58-3.50 (m, 1H), 3.45 (s, 3H), 3.30-3.28 (m, 1H), 3.11-3.05 (m, 2H), 2.81-2.79 (m, 1H), 1.90-1.88 (m, 1H), 1.76-1.69 (m, 3H), 1.54-1.50 (m, 2H), 0.97 (t, J=7.4Hz, 3H).

MS (ESI+) 523 (M^+1 , 100%) .

Example 70

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.25 (br, 3H), 7.51 (d, J=7.5Hz, 1H), 7.39-7.25 (m, 3H), 6.91-6.84 (m, 3H), 6.79 (d, J=7.3Hz, 1H), 5.44 (s, 2H), 3.98 (t, J=6.4Hz, 2H), 3.59-3.55 (m, 1H), 3.46 (s, 3H), 3.29-3.27 (m, 1H), 3.11-3.04 (m, 2H), 2.84-2.78 (m, 1H), 1.92-1.90 (m, 1H), 1.73-1.66 (m, 3H), 1.53-1.38 (m, 4H), 0.94 (t, J=7.3Hz, 3H).

MS (ESI+) 537 (M^+1 , 100%) .

Example 71

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.21 (br, 3H), 7.50 (d, J=7.5Hz, 1H), 7.38-7.24 (m, 3H), 6.90-6.77 (m, 4H), 5.43 (s, 2H), 3.76-3.73 (m, 2H), 3.59-3.56 (m, 1H), 3.45 (s, 3H), 3.29-3.26 (m, 1H), 3.09-3.02 (m, 2H), 2.81-

2.79 (m, 1H), 2.06-1.89 (m, 2H), 1.69-1.66 (m, 1H), 1.52-1.46 (m, 2H), 0.97 (d, J=5.6Hz, 6H).

MS (ESI+) 537 (M⁺+1, 100%).

Example 72

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.32 (br, 3H), 7.50 (d, J=7.5Hz, 1H), 7.37-7.24 (m, 3H), 6.89-6.83 (m, 3H), 6.78 (d, J=7.1Hz, 1H), 5.44 (s, 2H), 3.81 (d, J=7.0Hz, 2H), 3.55-3.51 (m, 1H), 3.45 (s, 3H), 3.27-3.25 (m, 1H), 3.10-3.04 (m, 2H), 2.80-2.78 (m, 1H), 1.90-1.87 (m, 1H), 1.69-1.67 (m, 1H), 1.53-1.35 (m, 2H), 1.23-1.21 (m, 1H), 0.55-0.53 (m, 2H), 0.34-0.31 (m, 2H).

MS (ESI+) 535 (M⁺+1, 100%).

Example 73

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.08 (br, 3H), 7.52-7.49 (m, 1H), 7.41-7.24 (m, 3H), 7.03-6.98 (m, 2H), 6.90-6.87 (m, 1H), 6.78-6.75 (m, 1H), 5.43 (s, 2H), 3.88-3.84 (m, 1H), 3.52-3.47 (m, 1H), 3.45 (s, 3H), 3.29-3.27 (m, 1H), 3.07-3.03 (m, 2H), 2.81-2.78 (m, 1H), 1.92-1.89 (m, 1H), 1.70-1.68 (m, 1H), 1.51-1.46 (m, 2H), 0.80-0.76 (m, 2H), 0.69-0.65 (m, 2H).

MS (ESI+) 521 (M⁺+1, 100%).

Example 74

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.20-8.13 (m, 3H), 7.51 (d, J=7.5Hz, 1H), 7.37-7.24 (m, 3H), 6.90-6.76 (m, 4H), 5.43 (s, 2H), 4.73-4.64 (m, 1H), 3.52-3.50 (m, 1H), 3.45-3.43 (m, 1H), 3.44 (s, 3H), 3.05-3.01 (m, 2H), 2.83-2.76 (m, 1H), 2.44-2.41 (m, 2H), 2.07-2.01 (m, 2H), 1.90-1.87 (m, 1H), 1.82-1.47 (m, 5H).

MS (ESI+) 535 (M⁺+1, 100%).

Example 75

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.33 (br, 3H), 7.52 (d, J=7.5Hz, 1H), 7.36-7.26 (m, 2H), 7.00-6.96 (m, 2H), 6.83-6.74 (m, 2H), 6.10 (s, 2H), 5.45 (s, 2H), 3.57-3.54 (m, 1H), 3.45 (s, 3H), 3.30-3.27 (m, 1H), 3.14-3.04 (m, 2H), 2.86-2.80 (m, 1H), 1.92-1.90 (m, 1H), 1.71-1.69 (m, 1H), 1.58-1.46

(m, 2H).

MS (ESI+) 509 (M^+1 , 34%) .

Example 76

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.36 (br, 3H), 7.58-7.50 (m, 2H), 7.36-7.16 (m, 6H), 6.82 (d, $J=6.4\text{Hz}$, 1H), 5.46 (d, $J=18.1\text{Hz}$, 2H), 3.60-3.55 (m, 1H), 3.47 (s, 3H), 3.29-3.27 (m, 1H), 3.14-3.04 (m, 2H), 2.86-2.79 (m, 1H), 1.92-1.90 (m, 1H), 1.71-1.46 (m, 3H).

MS (ESI+) 531 (M^+1 , 100%) .

Example 77

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.22 (br, 3H), 7.62 (t, $J=8.2\text{Hz}$, 1H), 7.52-7.45 (m, 2H), 7.41-7.24 (m, 4H), 6.78-6.76 (m, 1H), 5.44 (s, 2H), 3.54-3.50 (m, 1H), 3.46 (s, 3H), 3.28-3.26 (m, 1H), 3.09-3.02 (m, 2H), 2.80-2.78 (m, 1H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.52-1.47 (m, 2H).

MS (ESI+) 549 (M^+1 , 33%) .

Example 78

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.35 (br, 3H), 7.50 (d, $J=7.5\text{Hz}$, 1H), 7.40 (t, $J=8.1\text{Hz}$, 1H), 7.34-7.24 (m, 2H), 7.03-6.93 (m, 3H), 6.85-6.80 (m, 1H), 6.59-6.57 (m, 0.25H), 6.40-6.38 (m, 0.5H), 6.22-6.20 (m, 0.25H), 5.44 (t, $J=18.4\text{Hz}$, 2H), 4.38-4.27 (m, 2H), 3.58-3.53 (m, 1H), 3.45 (s, 3H), 3.28-3.26 (m, 1H), 3.13-3.06 (m, 2H), 2.82-2.80 (m, 1H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.54-1.34 (m, 2H).

MS (ESI+) 545 (M^+1 , 100%) .

Example 79

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.36 (br, 3H), 7.51-7.40 (m, 2H), 7.34-7.25 (m, 2H), 7.09-6.98 (m, 3H), 6.85-6.80 (m, 1H), 5.44 (t, $J=18.3\text{Hz}$, 2H), 4.80 (dd, $J=8.9, 17.7\text{Hz}$, 2H), 3.58-3.53 (m, 1H), 3.45 (s, 3H), 3.29-3.27 (m, 1H), 3.13-3.06 (m, 2H), 2.82-2.80 (m, 1H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.54-1.34 (m, 2H).

MS (ESI+) 563 (M^+1 , 100%) .

Example 80

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.34 (br, 3H), 7.59 (t, J=8.5Hz, 1H), 7.52-7.48 (m, 1H), 7.36-7.26 (m, 5H), 7.03-7.01 (m, 0.25H), 6.86-6.84 (m, 0.5H), 6.82-6.79 (m, 1H), 6.68-6.66 (m, 0.25H), 5.44 (t, J=18.5Hz, 2H), 3.57-3.53 (m, 1H), 3.45 (s, 3H), 3.27-3.25 (m, 1H), 3.13-3.02 (m, 2H), 2.81-2.79 (m, 1H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.53-1.44 (m, 2H).

MS (ESI+) 581 (M⁺+1, 100%).

Example 81

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.23 (br, 3H), 7.52-7.49 (m, 1H), 7.39 (t, J=8.1Hz, 1H), 7.34-7.24 (m, 2H), 7.05-7.00 (m, 2H), 6.94-6.91 (m, 1H), 6.79-6.77 (m, 1H), 5.43 (s, 2H), 4.96-4.56 (m, 5H), 3.52-3.50 (m, 1H), 3.45 (s, 3H), 3.29-3.27 (m, 1H), 3.10-3.03 (m, 2H), 2.81-2.79 (m, 1H), 1.89-1.87 (m, 1H), 1.68-1.66 (m, 1H), 1.50-1.46 (m, 2H).

MS (ESI+) 559 (M⁺+1, 100%).

Example 82

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.21 (br, 3H), 7.52-7.42 (m, 2H), 7.34-7.24 (m, 2H), 7.03-6.98 (m, 3H), 6.78 (d, J=7.1Hz, 1H), 5.44 (s, 2H), 4.57-4.55 (m, 1H), 3.58-3.54 (m, 1H), 3.47 (s, 3H), 3.28-3.26 (m, 1H), 3.09-3.02 (m, 2H), 2.81-2.79 (m, 1H), 2.10-2.04 (m, 1H), 1.90-1.75 (m, 3H), 1.50-1.46 (m, 2H).

MS (ESI+) 557 (M⁺+1, 100%).

Example 83

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.24-8.19 (m, 3H), 7.51 (dd, J=1.4, 7.8Hz, 1H), 7.38 (t, J=8.2Hz, 1H), 7.33-7.28 (m, 2H), 6.93-6.88 (m, 3H), 6.79 (d, J=8.9Hz, 1H), 5.44 (s, 2H), 4.71 (s, 2H), 3.54-3.48 (m, 1H), 3.46 (m, 3H), 3.35-3.30 (m, 1H), 3.10-3.05 (m, 2H), 2.83-2.79 (m, 1H), 1.70-1.67 (m, 1H), 1.59-1.52 (m, 1H), 1.45-1.44 (m, 2H).

MS (ESI+) 539 (M⁺+1, 100%).

Example 84

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.19 (br, 3H), 7.52 (dd, J=1.4, 7.8Hz, 1H),

7.41-7.29 (m, 4H), 6.97-6.96 (m, 1H), 6.94-6.90 (m, 1H), 6.79-6.77 (m, 1H), 5.45 (s, 2H), 4.84 (s, 2H), 3.72 (s, 3H), 3.68-3.55 (m, 1H), 3.47 (s, 3H), 3.35-3.30 (m, 1H), 3.10-3.05 (m, 2H), 3.04-3.00 (m, 1H), 1.91-1.89 (m, 1H), 1.71-1.69 (m, 1H), 1.55-1.45 (m, 2H).

MS (ESI+) 553 (M^+1 , 100%).

Example 85

^1H NMR (400MHz, DMSO- d_6) δ ppm 8.19 (br, 3H), 7.52 (dd, $J=1.4$, 7.8Hz, 1H), 7.34-7.28 (m, 2H), 7.22 (dd, $J=2.3$, 6.8Hz, 2H), 7.02 (dd, $J=2.3$, 6.8Hz, 2H), 6.79 (dd, $J=1.2$, 7.4Hz, 1H), 5.44 (s, 2H), 4.85 (s, 2H), 3.72 (s, 3H), 3.56-3.46 (m, 1H), 3.47 (s, 3H), 3.35-3.25 (m, 1H), 3.10-2.83 (m, 2H), 2.83-2.73 (m, 1H), 1.91-1.85 (m, 1H), 1.69-1.67 (m, 1H), 1.55-1.46 (m, 2H).

MS (ESI+) 553 (M^+1 , 100%).

Example 86

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.17 (br, 3H), 7.52 (d, $J=7.7$ Hz, 1H), 7.43 (t, $J=7.9$ Hz, 1H), 7.36-7.23 (m, 4H), 7.15 (d, $J=7.9$ Hz, 1H), 6.78 (d, $J=7.5$ Hz, 1H), 5.44 (s, 2H), 4.55 (s, 2H), 3.54-3.52 (m, 1H), 3.47 (s, 3H), 3.31-3.29 (m, 1H), 3.09-3.02 (m, 2H), 2.85-2.78 (m, 1H), 1.91-1.89 (m, 1H), 1.69-1.67 (m, 1H), 1.54-1.47 (m, 2H).

MS (ESI+) 495 (M^+1 , 100%).

Example 87

^1H NMR (400MHz, DMSO- d_6) δ ppm 8.41 (br, 3H), 8.06 (d, $J=8.6$ Hz, 2H), 7.62 (d, $J=8.7$ Hz, 2H), 7.53-7.51 (m, 1H), 7.35-7.26 (m, 2H), 6.79 (d, $J=6.4$ Hz, 1H), 5.43 (s, 2H), 3.55-3.52 (m, 1H), 3.50 (s, 3H), 3.31 (s, 3H), 3.30-3.29 (m, 1H), 3.01-3.08 (m, 2H), 2.83-2.76 (m, 1H), 1.95-1.88 (m, 1H), 1.73-1.65 (m, 1H), 1.63-1.38 (m, 2H).

MS (ESI+) 543 (M^+1 , 100%).

Example 88

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.23 (br, 3H), 7.51-7.49 (m, 1H), 7.37-7.27 (m, 3H), 6.89-6.86 (m, 1H), 6.80-6.79 (m, 1H), 6.88 (t, $J=2.3$ Hz, 1H),

6.53-6.50 (m, 1H), 5.44 (s, 2H), 4.16 (dd, J=7.0, 14.2Hz, 2H), 3.55-3.50 (m, 1H), 3.44 (s, 3H), 3.28-3.26 (m, 1H), 3.07-3.04 (m, 2H), 2.80-2.68 (m, 3H), 2.41-2.36 (m, 2H), 1.94-1.90 (m, 3H), 1.70-1.67 (m, 1H), 1.55-1.44 (m, 2H), 1.12 (t, J=7.1Hz, 3H).

MS (ESI+) 607 (M⁺+1, 100%).

Example 89

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.08-8.04 (m, 5H), 7.52 (dd, J=1.4, 7.8Hz, 1H), 7.45-7.43 (m, 2H), 7.34-7.28 (m, 2H), 6.77 (d, J=7.5Hz, 1H), 5.44 (s, 2H), 3.55-3.50 (m, 1H), 3.48 (s, 3H), 3.35-3.29 (m, 1H), 3.08-3.01 (m, 2H), 2.82-2.80 (m, 1H), 1.91-1.88 (m, 1H), 1.69-1.68 (m, 1H), 1.47-1.44 (m, 2H).

MS (ESI+) 509 (M⁺+1, 100%).

Example 90

¹H NMR (400MHz, DMSO-d₆) δ ppm 7.99 (br, 3H), 7.94-7.89 (m, 2H), 7.66-7.62 (m, 2H), 7.53-7.51 (m, 1H), 7.33-7.28 (m, 2H), 6.77 (dd, J=1.4, 7.9Hz, 1H), 5.44 (s, 2H), 3.89 (s, 3H), 3.49 (s, 3H), 3.50-3.40 (m, 1H), 3.35-3.25 (m, 1H), 3.06-3.01 (m, 2H), 2.81-2.78 (m, 1H), 1.69-1.61 (m, 1H), 1.92-1.89 (m, 1H), 1.52-1.44 (m, 2H).

MS (ESI+) 523 (M⁺+1, 100%).

Example 91

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.11 (m, 3H), 7.52 (dd, J=1.4, 7.8Hz, 1H), 7.40-7.28 (m, 6H), 7.29 (t, J_{H-F}=74.0Hz, 1H), 6.77 (d, J=6.2Hz, 1H), 5.45 (s, 2H), 3.50-3.47 (m, 1H), 3.47 (s, 3H), 3.40-3.30 (m, 1H), 3.08-3.02 (m, 2H), 2.85-2.79 (m, 1H), 1.90-1.85 (m, 1H), 1.68-1.60 (m, 1H), 1.51-1.46 (m, 2H).

MS (ESI+) 531 (M⁺+1, 100%).

Example 92

¹H NMR (400 MHz, MeOH-d₄) δ ppm 7.50-7.44 (m, 1H), 7.36-7.08 (m, 4H), 6.84-6.74 (m, 2H), 5.56 (s, 2H), 4.89-4.70 (m, 1H), 3.78 (s, 3H), 3.68-3.60 (m, 2H), 3.58 (s, 3H), 3.44-3.34 (m, 1H), 3.26-3.18 (m, 1H), 3.05-

2.92 (m, 1H), 2.90–2.79 (m, 1H), 2.78–2.66 (m, 1H), 2.30–2.12 (m, 2H), 2.10–2.01 (m, 1H), 1.84–1.72 (m, 1H), 1.68–1.53 (m, 2H).

MS (ESI+) 579 ($M^+ + 1$, 100%)

Example 93

^1H NMR (400 MHz, MeOH- d_4) δ ppm 7.50–7.13 (m, 9H), 5.56 (s, 2H), 3.80–3.69 (m, 1H), 3.55 (s, 3H), 3.44–3.34 (m, 1H), 3.31–3.22 (m, 1H), 3.15–3.00 (m, 2H), 2.12–2.00 (m, 1H), 1.89–1.75 (m, 1H), 1.70–1.51 (m, 2H).

MS (ESI+) 464 ($M^+ + 1$, 100%)

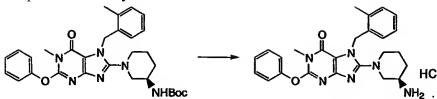
Example 94

^1H NMR (400 MHz, MeOH- d_4) δ ppm 7.48–7.40 (m, 1H), 7.38–7.05 (m, 7H), 6.98–6.88 (m, 1H), 5.58 (s, 2H), 4.31 (s, 2H), 3.78–3.69 (m, 1H), 3.68–3.59 (m, 2H), 3.65 (s, 3H), 3.49–3.36 (m, 1H), 3.05–2.95 (m, 1H), 2.13–2.00 (m, 1H), 1.82–1.70 (m, 1H), 1.69–1.52 (m, 2H)

MS (ESI+) 463 ($M^+ + 1$, 100%)

Example 95

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-methylbenzyl)-1-methyl-2-phenoxy-1,7-dihydro-6H-purine-6-one hydrochloride

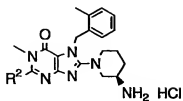


Compound 95 was synthesized from the compound of the corresponding reference example in the same manner as in Example 64.

^1H NMR (400MHz, DMSO- d_6) δ ppm 8.25 (br, 3H), 7.51–7.45 (m, 2H), 7.34–7.28 (m, 3H), 7.22–7.06 (m, 3H), 6.57 (d, $J=7.1\text{Hz}$, 1H), 5.41 (d, $J=17.2\text{Hz}$, 1H), 5.35 (d, $J=17.2\text{Hz}$, 1H), 3.56–3.53 (m, 1H), 3.46 (s, 3H), 3.30–3.27 (m, 1H), 3.10–3.03 (m, 2H), 2.83–2.76 (m, 1H), 2.33 (s, 3H), 1.91–1.88 (m, 1H), 1.68–1.65 (m, 1H), 1.54–1.40 (m, 2H).

MS (ESI+) 445 ($M^+ + 1$, 18%).

Compounds 96 through 105 were synthesized from the compounds of the corresponding reference examples in the same manner as in Example 95.



Example No.	R ²	Starting Material Reference Example No.
Example 96		Reference Example 114
Example 97		Reference Example 115
Example 98		Reference Example 116
Example 99		Reference Example 117
Example 100		Reference Example 118
Example 101		Reference Example 119
Example 102		Reference Example 120
Example 103		Reference Example 121
Example 104		Reference Example 122
Example 105		Reference Example 123

Example 96

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.23 (br, 3H), 7.26-7.06 (m, 4H), 6.74-6.68 (m, 3H), 6.57 (d, J=7.0Hz, 1H), 5.38 (s, 2H), 3.57-3.54 (m, 1H), 3.43 (s, 3H), 3.31-3.29 (m, 1H), 3.11-3.04 (m, 2H), 2.81-2.79 (m, 1H), 2.33 (s, 3H), 1.90-1.88 (m, 1H), 1.68-1.66 (m, 1H), 1.51-1.42 (m, 2H).

MS (ESI+) 461 (M⁺+1, 100%) .

Example 97

¹H NMR (300MHz, DMSO-d₆) δ ppm 7.83 (br, 3H), 7.36 (t, J=7.9Hz, 1H), 7.26-7.05 (m, 3H), 6.92-6.84 (m, 3H), 6.55 (d, J=7.1Hz, 1H), 5.41 (d, J=17.0Hz, 1H), 5.34 (d, J=17.0Hz, 1H), 3.77 (s, 3H), 3.54-3.51 (m, 1H), 3.44 (s, 3H), 3.23-3.17 (m, 1H), 3.04-2.97 (m, 2H), 2.80-2.74 (m, 1H), 2.33 (s, 3H), 1.90-1.84 (m, 1H), 1.69-1.60 (m, 1H), 1.51-1.40 (m, 2H).

MS (ESI+) 475 (M⁺+1, 14%) .

Example 98

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.18 (br, 3H), 7.36 (t, J=8.1Hz, 1H), 7.23-7.07 (m, 3H), 6.91-6.84 (m, 3H), 6.57 (d, J=7.3Hz, 1H), 5.38 (s, 2H), 4.04 (dd, J=6.8, 13.8Hz, 2H), 3.54-3.52 (m, 1H), 3.46 (s, 3H), 3.32-3.30 (m, 1H), 3.09-3.05 (m, 2H), 2.83-2.80 (m, 1H), 2.34 (s, 3H), 1.92-1.90 (m, 1H), 1.69-1.67 (m, 1H), 1.51-1.46 (m, 2H), 1.34 (t, J=6.9Hz, 3H).

MS (ESI+) 489 (M⁺+1, 100%) .

Example 99

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.18 (br, 3H), 7.35 (t, J=7.9Hz, 1H), 7.23-7.07 (m, 3H), 6.89-6.82 (m, 3H), 6.57 (d, J=7.5Hz, 1H), 5.38 (s, 2H), 4.66-4.58 (m, 1H), 3.57-3.55 (m, 1H), 3.46 (s, 3H), 3.32-3.30 (m, 1H), 3.10-3.03 (m, 2H), 2.83-2.77 (m, 1H), 2.34 (s, 3H), 1.92-1.90 (m, 1H), 1.69-1.67 (m, 1H), 1.54-1.43 (m, 2H), 1.28 (d, J=5.8Hz, 6H).

MS (ESI+) 503 (M⁺+1, 100%) .

Example 100

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.34 (br, 3H), 7.35 (t, J=8.2Hz, 1H), 7.23-7.07 (m, 3H), 6.88-6.83 (m, 3H), 6.60 (d, J=7.5Hz, 1H), 5.44 (d, J=16.9Hz, 1H), 5.36 (d, J=16.9Hz, 1H), 4.83-4.81 (m, 1H), 3.59-3.56 (m, 1H), 3.45 (s,

3H), 3.32-3.30 (m, 1H), 3.14-3.07 (m, 2H), 2.85-2.81 (m, 1H), 2.35 (s, 3H), 1.94-1.92 (m, 3H), 1.73-1.43 (m, 9H).

MS (ESI+) 529 ($M^+ + 1$, 100%).

Example 101

^1H NMR (400MHz, DMSO- d_6) δ ppm 8.47 (br, 3H), 7.48-7.42 (m, 3H), 7.19-7.10 (m, 7H), 7.09-7.08 (m, 1H), 6.98-6.95 (m, 1H), 6.62 (d, $J=7.6\text{Hz}$, 1H), 5.46 (d, $J=17.0\text{Hz}$, 1H), 5.37 (d, $J=17.0\text{Hz}$, 1H), 3.71-3.60 (m, 1H), 3.44 (s, 3H), 3.36-3.23 (m, 1H), 3.19-3.06 (m, 2H), 2.88-2.79 (m, 1H), 2.34 (s, 3H), 1.95-1.87 (m, 1H), 1.79-1.69 (m, 1H), 1.64-1.53 (m, 1H), 1.49-1.38 (m, 1H).

MS (ESI+) 537 ($M^+ + 1$, 100%).

Example 102

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.10 (br, 3H), 7.57-7.52 (m, 1H), 7.23-7.07 (m, 6H), 6.56 (d, $J=7.5\text{Hz}$, 1H), 5.38 (s, 2H), 3.61-3.56 (m, 1H), 3.47 (s, 3H), 3.28-3.27 (m, 2H), 3.08-3.01 (m, 2H), 2.81-2.79 (m, 1H), 2.34 (s, 3H), 1.92-1.90 (m, 1H), 1.67-1.65 (m, 1H), 1.53-1.46 (m, 2H).

MS (ESI+) 511 ($M^+ + 1$, 100%).

Example 103

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.32 (br, 3H), 7.62 (t, $J=8.2\text{Hz}$, 1H), 7.46-7.34 (m, 3H), 7.24-7.06 (m, 3H), 6.57 (d, $J=7.3\text{Hz}$, 1H), 5.43 (d, $J=17.0\text{Hz}$, 1H), 5.36 (d, $J=17.0\text{Hz}$, 1H), 3.58-3.55 (m, 1H), 3.46 (s, 3H), 3.27-3.25 (m, 1H), 3.11-3.04 (m, 2H), 2.83-2.76 (m, 1H), 2.34 (s, 3H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.53-1.41 (m, 2H).

MS (ESI+) 529 ($M^+ + 1$, 100%).

Example 104

^1H NMR (300MHz, DMSO- d_6) δ ppm 8.36 (br, 3H), 7.33-7.28 (m, 1H), 7.23-7.06 (m, 4H), 6.88-6.81 (m, 1H), 6.60 (d, $J=7.0\text{Hz}$, 1H), 5.42 (d, $J=16.9\text{Hz}$, 1H), 5.34 (d, $J=16.9\text{Hz}$, 1H), 3.76 (s, 3H), 3.59-3.53 (m, 1H), 3.45 (s, 3H), 3.28-3.20 (m, 1H), 3.13-2.95 (m, 2H), 2.90-2.75 (m, 1H), 2.33 (s, 3H), 1.90-1.84 (m, 1H), 1.70-1.63 (m, 1H), 1.56-1.49 (m, 1H), 1.44-1.36 (m,

1H).

MS (ESI+) 493 (M⁺+1, 100%) .

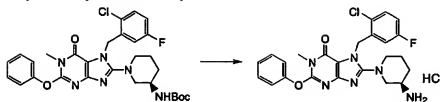
Example 105

¹H NMR (300MHz, DMSO-d₆) δ ppm 8.32 (br, 3H), 7.22-7.06 (m, 3H), 6.98-6.95 (m, 2H), 6.74 (dd, J=2.3, 8.2Hz, 1H), 6.57 (d, J=7.1Hz, 1H), 6.08 (s, 2H), 5.42 (d, J=17.1Hz, 1H), 5.35 (d, J=17.1Hz, 1H), 3.54-3.49 (m, 1H), 3.43 (s, 3H), 3.30-3.28 (m, 1H), 3.12-3.05 (m, 2H), 2.82-2.80 (m, 1H), 2.33 (s, 3H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.52-1.43 (m, 2H).

MS (ESI+) 489 (M⁺+1, 100%) .

Example 106

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chloro-5-fluorobenzyl)-1-methyl-2-phenoxy-1,7-dihydro-6H-purine-6-one hydrochloride

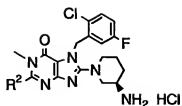


Compound 106 was synthesized from the compound of the corresponding reference example in the same manner as in Example 64.

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.00-7.99 (br, 3H), 7.52 (dd, J=5.1, 8.8Hz, 1H), 7.51-7.47 (m, 2H), 7.35-7.23 (m, 4H), 6.77 (dd, J=2.9, 9.3Hz, 1H), 5.39 (s, 2H), 3.48 (s, 3H), 3.42-3.32 (m, 2H), 3.06-2.84 (m, 2H), 2.70-2.63 (m, 1H), 1.92-1.89 (m, 1H), 1.75-1.70 (m, 1H), 1.52-1.48 (m, 2H).

MS (ESI+) 483 (M⁺+1, 100%) .

Compounds 107 and 108 were synthesized from the compounds of the corresponding reference examples in the same manner as in Example 64.



Example No.	R ²	Starting Material Reference Example No.
Example 107		Reference Example 125
Example 108		Reference Example 126

Example 107

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.18 (br, 3H), 7.60-7.57 (m, 1H), 7.41-7.36 (m, 1H), 7.25-7.22 (m, 1H), 6.93-6.86 (m, 3H), 6.71-6.68 (m, 1H), 5.40 (s, 2H), 3.79 (s, 3H), 3.52-3.49 (m, 1H), 3.47 (s, 3H), 3.32-3.30 (m, 1H), 3.11-3.03 (m, 2H), 2.86-2.82 (m, 1H), 1.92-1.90 (m, 1H), 1.75-1.71 (m, 1H), 1.59-1.46 (m, 2H).

MS (ESI+) 513 (M⁺+1, 100%).

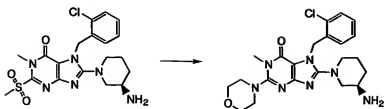
Example 108

¹H NMR (400MHz, DMSO-d₆) δ ppm 8.15 (br, 3H), 7.59-7.49 (m, 2H), 7.22-7.12 (m, 5H), 6.69-6.65 (m, 1H), 5.42 (d, J=17.9Hz, 1H), 5.37 (d, J=17.9Hz, 1H), 3.51-3.48 (m, 1H), 3.46 (s, 3H), 3.30-3.28 (m, 1H), 3.10-3.02 (m, 2H), 2.85-2.80 (m, 1H), 1.90-1.88 (m, 1H), 1.73-1.71 (m, 1H), 1.55-1.47 (m, 2H).

MS (ESI+) 549 (M⁺+1, 100%).

Example 109

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-2-morpholino-1,7-dihydro-6H-purine-6-one



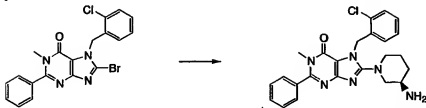
Morpholine (2 mL) was added to 8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-1,7-dihydro-6H-purine-6-one (10 mg), and the ingredients were heated and stirred for 20 hours at 100°C in a sealed tube. The reaction solution was cooled to 25°C, and toluene (20 mL) was then added before distillation at reduced pressure (repeated 3 times). The residue was purified by preparative thin layer chromatography (silica gel, chloroform/methanol = 8/1), giving the titled compound (5 mg).

¹H NMR (300MHz, CDCl₃) δ ppm 7.42–7.38 (m, 1H), 7.22–7.14 (m, 2H), 6.84–6.81 (d, J=7.5Hz, 1H), 5.51–5.50 (m, 2H), 3.87–3.83 (m, 4H), 3.54 (s, 3H), 3.46–3.45 (m, 1H), 3.31–3.30 (m, 1H), 3.23–3.20 (m, 4H), 2.97–2.93 (m, 2H), 2.76–2.68 (m, 1H), 1.80–1.74 (m, 3H), 1.26–1.24 (m, 1H).

MS (ESI+) 458 (M⁺+1, 49%) .

Example 110

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-2-phenyl-1,7-dihydro-6H-purine-6-one



(R)-tert-butylpiperidin-3-yl carbamate (291 mg) and diisopropylethylamine (0.304 mL) were added to an ethanol solution (2.0 mL) of 8-bromo-7-(2-chlorobenzyl)-1-methyl-2-phenyl-1,7-dihydro-6H-purine-6-one (250 mg), and the ingredients were sealed to be heated and stirred for 3 hours at 100°C. The ethanol was distilled off at reduced pressure, water and potassium carbonate were added to the residue, the solution was rendered alkaline, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was then

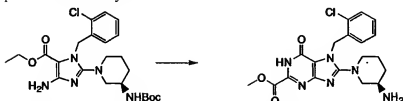
concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, chloroform/methanol = 20/1), giving an intermediate. The intermediate was dissolved in methanol (1.0 mL), 4 N hydrochloric acid/1,4-dioxane solution (4.3 mL) was added, and the reaction solution was stirred for 4 hours at room temperature. Water and potassium carbonate were added to the reaction solution, the solution was rendered alkaline, and it was extracted twice with ethyl acetate. The pooled organic layers were dried over anhydrous magnesium sulfate and filtered, and the filtrate was then concentrated at reduced pressure, giving the titled compound (44.1 mg).

¹H NMR (400 MHz, CDCl₃) δ ppm 7.59–7.54 (m, 2H), 7.52–7.47 (m, 3H), 7.47–7.42 (m, 1H), 7.27–7.22 (m, 2H), 6.92–6.87 (m, 1H), 5.61–5.56 (m, 2H), 3.60–3.55 (m, 1H), 3.46 (s, 3H), 3.33–3.28 (m, 1H), 2.97–2.92 (m, 1H), 2.90–2.85 (m, 2H), 1.95–1.90 (m, 1H), 1.70–1.65 (m, 1H), 1.47–1.42 (m, 1H), 1.30–1.25 (m, 1H).

MS (ESI+) 449 (M⁺+1, 100%)

Example 111

Methyl 8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-6,7-dihydro-1H-purine-2-carboxylate



Methyl cyanofornate (0.397 mL) and 4N hydrochloric acid/1,4-dioxane solution (10 mL) were added to a 1,4-dioxane solution (2 mL) of ethyl 4-amino-2-[(3R)-3-(tert-butoxycarbonyl)amino]piperidin-1-yl]-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylate (478 mg), and the contents were allowed to stand for 3 days at 25°C in a sealed tube and then heated and stirred for 10 hours at 70°C. The reaction solution was concentrated at reduced pressure, saturated sodium bicarbonate aqueous solution (50 mL) was added to the residue, and the solution was rendered alkaline and extracted 3 times with chloroform (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The residue was purified by column chromatography (silica gel, chloroform/methanol = 100/1 to 8/1), giving the titled compound (63 mg).

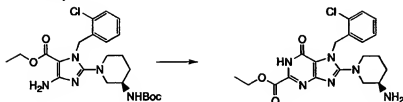
¹H NMR (300MHz, CDCl₃) δ ppm 7.42–7.38 (m, 1H), 7.29–7.17 (m, 2H), 6.82 (d, J=5.9Hz, 1H), 5.56 (s, 2H), 4.03 (s, 3H), 3.80–3.76 (m, 1H), 3.34–3.41 (

m, 1H), 3.31-3.20 (m, 2H), 3.02-2.95 (m, 1H), 2.12-2.10 (m, 1H), 1.74-1.72 (m, 2H), 1.59-1.57 (m, 1H).

MS (ESI+) 417 ($M^+ + 1$, 100%).

Example 112

Ethyl 8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-6,7-dihydro-1H-purinee-2-carboxylate



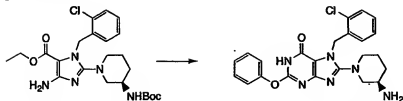
The compound of Example 112 was synthesized from the compound of the corresponding reference example in the same manner as in Example 111.

^1H NMR (300MHz, CDCl_3) δ ppm 7.40-7.37 (m, 1H), 7.25-7.15 (m, 2H), 6.82 (d, $J=7.3\text{Hz}$, 1H), 5.57 (s, 2H), 4.47 (dd, $J=7.1$, 14.3Hz, 2H), 3.79-3.74 (m, 1H), 3.35-3.19 (m, 2H), 3.14-2.90 (m, 2H), 2.08-2.06 (m, 1H), 1.74-1.61 (m, 3H), 1.44-1.40 (t, $J=7.0\text{Hz}$, 3H).

MS (ESI+) 431 ($M^+ + 1$, 100%).

Example 113

8-[(3R)-3-aminopiperidin-1-yl]-7-(2-chloro-5-fluorobenzyl)-2-phenoxy-1,7-dihydro-6H-purinee-6-one



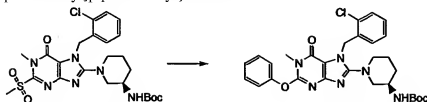
The compound of Example 113 was synthesized from the compound of the corresponding reference example in the same manner as in Example 111.

^1H NMR (300MHz, CDCl_3) δ ppm 7.53-7.21 (m, 9H), 6.85-6.83 (m, 1H), 5.49 (s, 2H), 3.41-3.37 (m, 1H), 3.23-3.21 (m, 1H), 2.89-2.86 (m, 2H), 2.72-2.69

(m, 1H), 1.87–1.85 (m, 1H), 1.64–1.53 (m, 2H), 1.25–1.23 (m, 1H).
 MS (ESI+) 451 (M⁺+1, 100%) .

Reference Example 31

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate

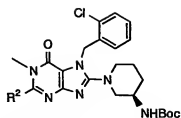


60% sodium hydride dispersion (0.56 g) was added to a tetrahydrofuran solution (40 mL) of phenol (1.45 g), and the contents were stirred for 1 hour at 25°C. A tetrahydrofuran solution (10 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (3.85 g) was added in the form of drops to the reaction solution, and the ingredients were stirred for 3 hours at 25°C. Saturated ammonium chloride aqueous solution (50 mL) was added to the reaction solution, and the tetrahydrofuran was distilled off at reduced pressure before extraction 3 times with chloroform (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 10/1 to 1/1), giving the titled compound (4.30 g).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.43–7.38 (m, 3H), 7.28–7.15 (m 5H), 6.76 (d, J=7.3Hz, 1H), 5.59 (d, J=17.0Hz, 1H), 5.49 (d, J=17.0Hz, 1H), 4.78–4.76 (m, 1H), 3.72–3.70 (m, 1H), 3.63 (s, 3H), 3.39–3.34 (m, 1H), 3.00–2.93 (m, 3H), 1.71–1.40 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 565 (M⁺+1, 100%) .

The compounds of Reference Examples 32 through 39, 57, 59 through 66, and 80 through 112 were synthesized in the same manner as in Reference Example 31.



Reference Example No.	R ²	Reference Example No.	R ²
Reference Example 32		Reference Example 62	
Reference Example 33		Reference Example 63	
Reference Example 34		Reference Example 64	
Reference Example 35		Reference Example 65	
Reference Example 36		Reference Example 66	
Reference Example 37			
Reference Example 38		Reference Example 80	
Reference Example 39		Reference Example 81	
Reference Example 57		Reference Example 82	
Reference Example 59		Reference Example 83	
Reference Example 60		Reference Example 84	
Reference Example 61			

Reference Example No.	R ²	Reference Example No.	R ²
Reference Example 85		Reference Example 96	
Reference Example 86		Reference Example 97	
Reference Example 87		Reference Example 98	
Reference Example 88		Reference Example 99	
Reference Example 89		Reference Example 100	
Reference Example 90		Reference Example 101	
Reference Example 91		Reference Example 102	
Reference Example 92		Reference Example 103	
Reference Example 93		Reference Example 104	
Reference Example 94		Reference Example 105	
Reference Example 95			

Reference Example No.	R ²	Reference Example No.	R ²
Reference Example 106		Reference Example 109	
Reference Example 107		Reference Example 110	
Reference Example 108		Reference Example 111	
		Reference Example 112	

Reference Example 32

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42–7.38 (m, 1H), 7.24–7.15 (m, 2H), 6.80–6.74 (m, 3H), 6.66–6.63 (m, 1H), 6.00 (s, 2H), 5.59 (d, J=17.1Hz, 1H), 5.49 (d, J=17.1Hz, 1H), 4.78–4.76 (m, 1H), 3.73–3.71 (m, 1H), 3.60 (s, 3H), 3.40–3.35 (m, 1H), 3.01–2.94 (m, 3H), 1.66–1.40 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 609 (M⁺+1, 100%).

Reference Example 33

¹H NMR (300 MHz, CDCl₃) δ ppm 8.55–8.52 (m, 2H), 7.68–7.65 (m, 1H), 7.42–7.36 (m, 2H), 7.22–7.16 (m, 2H), 6.77 (d, J=7.3Hz, 1H), 5.59 (d, J=16.9Hz, 1H), 5.50 (d, J=16.9Hz, 1H), 4.75–4.73 (m, 1H), 3.72–3.70 (m, 1H), 3.65 (s, 3H), 3.41–3.38 (m, 1H), 3.06–2.93 (m, 3H), 1.73–1.40 (m, 4H), 1.40 (s, 9H).

Reference Example 32

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42–7.34 (m, 3H), 7.22–7.01 (m, 9H), 6.76 (d, J=7.1Hz, 1H), 5.60 (d, J=17.0Hz, 1H), 5.50 (d, J=17.0Hz, 1H), 4.77–4.75 (m, 1H), 3.76–3.74 (m, 1H), 3.62 (s, 3H), 3.40–3.36 (m, 1H), 3.04–2.95 (m, 3H), 1.72–1.40 (m, 4H), 1.40 (s, 9H).

Reference Example 35

¹H NMR (400MHz, CDCl₃) δ ppm 7.41-7.36 (m, 3H), 7.20-7.17 (m, 4H), 6.75 (d, J=7.3Hz, 1H), 5.57-5.52 (m, 2H), 4.83-4.78 (m, 1H), 3.77-3.72 (m, 1H), 3.61 (s, 3H), 3.38 (dd, J=3.4, 12.6Hz, 1H), 3.06-2.95 (m, 3H), 1.75-1.45 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 599 (M⁺+1, 66%).

Reference Example 36

¹H NMR (400MHz, CDCl₃) δ ppm 7.40 (d, J=7.7Hz, 1H), 7.21-7.17 (m, 4H), 7.14-7.09 (m, 2H), 6.75 (d, J=7.4Hz, 1H), 5.59-5.54 (m, 2H), 4.83-4.78 (m, 1H), 3.77-3.72 (m, 1H), 3.62 (s, 3H), 3.37 (dd, J=3.4, 12.4Hz, 1H), 3.04-2.95 (m, 3H), 1.75-1.45 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 583 (M⁺+1, 67%).

Reference Example 57

¹H NMR (300 MHz, CDCl₃) δ ppm 7.96-7.94 (m, 1H), 7.86 (s, 1H), 7.52-7.39 (m, 3H), 7.22-7.16 (m, 2H), 6.76 (d, J=7.0Hz, 1H), 5.59 (d, J=16.9Hz, 1H), 5.50 (d, J=16.9Hz, 1H), 4.76-4.74 (m, 1H), 3.92 (s, 3H), 3.72-3.70 (m, 1H), 3.64 (s, 3H), 3.40-3.35 (m, 1H), 3.03-2.92 (m, 3H), 1.75-1.41 (m, 4H), 1.40 (s, 9H).

Reference Example 59

MS (ESI+) 637 (M⁺+1, 96%).

Reference Example 60

MS (ESI+) 649 (M⁺+1, 92%).

Reference Example 61

¹H NMR (300 MHz, CDCl₃) δ ppm 7.44-7.17 (m, 7H), 6.80-6.77 (m, 1H), 5.59 (d, J=17.1Hz, 1H), 5.49 (d, J=17.1Hz, 1H), 4.75-4.73 (m, 1H), 3.72-3.70 (m, 1H), 3.64 (s, 3H), 3.40-3.35 (m, 1H), 3.00-2.94 (m, 3H), 1.71-1.60 (m, 4H), 1.40 (s, 9H).

Reference Example 62

¹H NMR (300 MHz, CDCl₃) δ ppm 7.59-7.51 (m, 4H), 7.42-7.39 (m, 1H), 7.23-7.16 (m, 2H), 6.76 (d, J=9.0Hz, 1H), 5.59 (d, J=17.1Hz, 1H), 5.49 (d, J=17.1Hz, 1H), 4.72-4.70 (m, 1H), 3.73-3.71 (m, 1H), 3.63 (s, 3H), 3.42-3.38 (

n, 1H), 3.06-2.93 (m, 3H), 1.73-1.48 (m, 4H), 1.40 (s, 9H).

Reference Example 63

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42-7.33 (m, 2H), 7.22-7.15 (m, 2H), 7.05-6.96 (m, 3H), 6.75 (d, J=7.9Hz, 1H), 5.59 (d, J=17.0Hz, 1H), 5.49 (d, J=17.0Hz, 1H), 4.78-4.76 (m, 1H), 3.72-3.70 (m, 1H), 3.61 (s, 3H), 3.41-3.36 (m, 1H), 3.01-2.94 (m, 3H), 1.74-1.61 (m, 4H), 1.40 (s, 9H).

Reference Example 64

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42-7.39 (m, 1H), 7.32-7.15 (m, 3H), 6.84-6.75 (m, 4H), 5.59 (d, J=16.8Hz, 1H), 5.49 (d, J=16.8Hz, 1H), 4.76-4.74 (m, 1H), 3.81 (s, 3H), 3.74-3.72 (m, 1H), 3.62 (s, 3H), 3.39-3.34 (m, 1H), 3.02-2.94 (m, 3H), 1.71-1.58 (m, 4H), 1.40 (s, 9H).

Reference Example 65

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42-7.38 (m, 1H), 7.22-7.15 (m, 2H), 6.78-6.75 (m, 1H), 6.37 (s, 3H), 5.59 (d, J=17.1Hz, 1H), 5.49 (d, J=17.1Hz, 1H), 4.75-4.73 (m, 1H), 3.78 (s, 6H), 3.73-3.71 (m, 1H), 3.61 (s, 3H), 3.40-3.35 (m, 1H), 3.02-2.94 (m, 3H), 1.76-1.59 (m, 4H), 1.40 (s, 9H).

Reference Example 66

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42-7.38 (m, 1H), 7.30-7.15 (m, 3H), 6.80-6.71 (m, 4H), 5.59 (d, J=16.9Hz, 1H), 5.49 (d, J=16.9Hz, 1H), 4.73-4.71 (m, 1H), 3.87-3.83 (m, 4H), 3.73-3.71 (m, 1H), 3.61 (s, 3H), 3.38-3.35 (m, 1H), 3.19-3.16 (m, 4H), 2.99-2.93 (m, 3H), 1.74-1.46 (m, 4H), 1.40 (s, 9H).

Reference Example 80

MS (ESI⁺) 595 (M⁺+1, 100%).

Reference Example 81

MS (ESI⁺) 595 (M⁺+1, 92%).

Reference Example 82

MS (ESI⁺) 633 (M⁺+1, 75%).

Reference Example 83

MS (ESI⁺) 625 (M⁺+1, 85%).

Reference Example 84

MS (ESI+) 639 ($M^+ + 1$, 85%) .

Reference Example 85

MS (ESI+) 623 ($M^+ + 1$, 80%) .

Reference Example 86

MS (ESI+) 623 ($M^+ + 1$, 60%) .

Reference Example 87

MS (ESI+) 623 ($M^+ + 1$, 100%) .

Reference Example 88

MS (ESI+) 649 ($M^+ + 1$, 53%) .

Reference Example 89

MS (ESI+) 609 ($M^+ + 1$, 100%) .

Reference Example 90

MS (ESI+) 581 ($M^+ + 1$, 75%) .

Reference Example 91

MS (ESI+) 623 ($M^+ + 1$, 90%) .

Reference Example 92

MS (ESI+) 623 ($M^+ + 1$, 76%) .

Reference Example 93

MS (ESI+) 637 ($M^+ + 1$, 90%) .

Reference Example 94

MS (ESI+) 637 ($M^+ + 1$, 100%) .

Reference Example 95

MS (ESI+) 635 ($M^+ + 1$, 71%) .

Reference Example 96

^1H NMR (300MHz, CDCl_3) δ ppm 7.42–7.38 (m, 1H), 7.32–7.15 (m, 3H), 6.96–6.75 (m, 4H), 5.59 (d, $J=17.0\text{Hz}$, 1H), 5.49 (d, $J=17.0\text{Hz}$, 1H), 4.75–4.73 (m, 1H), 3.74–3.72 (m, 2H), 3.62 (s, 3H), 3.38–3.35 (m, 1H), 3.02–2.98 (m, 3H), 1.78–1.41 (m, 4H), 1.40 (s, 9H), 0.79–0.78 (m, 4H) .

MS (ESI+) 621 ($M^+ + 1$, 82%) .

Reference Example 97

MS (ESI+) 635 ($M^+ + 1$, 87%) .

Reference Example 98

MS (ESI+) 631 ($M^+ + 1$, 87%) .

Reference Example 99

MS (ESI+) 645 ($M^+ + 1$, 100%) .

Reference Example 100

MS (ESI+) 663 ($M^+ + 1$, 100%) .

Reference Example 101

MS (ESI+) 681 ($M^+ + 1$, 100%) .

Reference Example 102

MS (ESI+) 659 ($M^+ + 1$, 100%) .

Reference Example 103

MS (ESI+) 657 ($M^+ + 1$, 87%) .

Reference Example 104

MS (ESI+) 639 ($M^+ + 1$, 58%) .

Reference Example 105

MS (ESI+) 653 ($M^+ + 1$, 80%) .

Reference Example 106

MS (ESI+) 653 ($M^+ + 1$, 80%) .

Reference Example 107

MS (ESI+) 595 ($M^+ + 1$, 76%) .

Reference Example 108

MS (ESI+) 643 ($M^+ + 1$, 40%) .

Reference Example 109

MS (ESI+) 707 ($M^+ + 1$, 100%) .

Reference Example 110

MS (ESI+) 609 ($M^+ + 1$, 75%) .

Reference Example 111

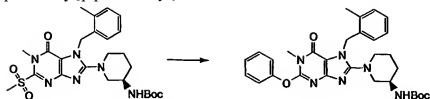
MS (ESI+) 631 ($M^+ + 1$, 90%) .

Reference Example 112

MS (ESI+) 679 ($M^+ + 1$, 100%) .

Reference Example 113

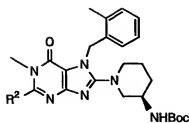
Tert-butyl{(3R)-1-[7-(2-methylbenzyl)-1-methyl-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



The compound of Reference Example 113 was synthesized from the compound of the corresponding reference example in the same manner as in Reference Example 31.

MS (ESI+) 545 ($M^+ + 1$, 88%) .

The compounds of Reference Examples 114 through 123 were synthesized from the compounds of the corresponding reference examples in the same manner as in Reference Example 113.



Reference Example No.	R ²	Reference Example No.	R ²
Reference Example 114		Reference Example 119	
Reference Example 115		Reference Example 120	
Reference Example 116		Reference Example 121	
Reference Example 117		Reference Example 122	
Reference Example 118		Reference Example 123	

Reference Example 114

MS (ESI+) 561 (M⁺+1, 81%) .

Reference Example 115

MS (ESI+) 575 (M⁺+1, 100%) .

Reference Example 116

MS (ESI+) 589 (M⁺+1, 100%) .

Reference Example 117

MS (ESI+) 603 (M⁺+1, 100%) .

Reference Example 118

MS (ESI+) 629 (M⁺+1, 100%) .

Reference Example 119

MS (ESI+) 637 (M⁺+1, 70%) .

Reference Example 120

MS (ESI+) 611 ($M^+ + 1$, 100%) .

Reference Example 121

MS (ESI+) 629 ($M^+ + 1$, 100%) .

Reference Example 122

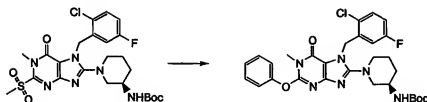
MS (ESI+) 593 ($M^+ + 1$, 100%) .

Reference Example 123

MS (ESI+) 589 ($M^+ + 1$, 100%) .

Reference Example 124

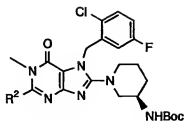
Tert-butyl[(3R)-1-[7-(2-chloro-5-fluorobenzyl)-1-methyl-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate



The compound of Reference Example 124 was synthesized from the compound of the corresponding reference example in the same manner as in Reference Example 31.

MS (ESI+) 583 ($M^+ + 1$, 54%) .

The compounds of Reference Examples 125 and 126 were synthesized from the compounds of the corresponding reference examples in the same manner as in Reference Example 31.



Reference Example No.

R²

Reference Example 125



Reference Example 126



Reference Example 125

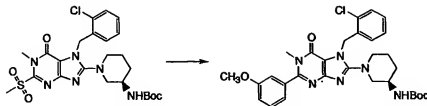
MS (ESI+) 613 (M⁺+1, 100%) .

Reference Example 126

MS (ESI+) 649 (M⁺+1, 100%) .

Reference Example 40

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-2-(3-methoxyphenyl)-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



A 1M tetrahydrofuran solution (0.79 mL) of 3-methoxyphenyl magnesium bromide was added at 0°C to tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (110 mg), the ingredients were stirred for 30 minutes, the temperature was increased to 25°C, and the content were stirred for 3 hours. A 1M tetrahydrofuran solution (1.58 mL) of 3-methoxyphenyl magnesium bromide was again added at 0°C, the contents were stirred for 30 minutes, the temperature was then increased to 25°C, and the contents were stirred for 3 hours.

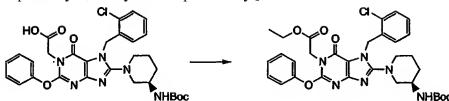
Saturated ammonium chloride aqueous solution (50 mL) was added to the reaction solution, and the tetrahydrofuran was distilled off at reduced pressure before extraction 3 times with chloroform (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by preparative thin layer chromatography (silica gel, chloroform/methanol = 30/1), giving the titled compound (118 mg).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.41–7.34 (m, 2H), 7.21–7.18 (m, 2H), 7.11–7.01 (m, 3H), 6.84–6.82 (m, 1H), 5.66 (d, J=17.0Hz, 1H), 5.55 (d, J=17.0Hz, 1H), 4.86–4.84 (m, 1H), 3.82 (s, 3H), 3.74–3.72 (m, 1H), 3.47 (s, 3H), 3.47–3.43 (m, 1H), 3.10–3.03 (m, 3H), 2.07–2.05 (m, 1H), 1.75–1.43 (m, 3H), 1.42 (s, 9H).

MS (ESI+) 579 (M⁺+1, 19%).

Reference Example 41

Ethyl[8-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-7-(2-chlorobenzyl)-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-1-yl]acetate



Ethanol (0.083 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (169 mg), 1-hydroxybenzotriazole (119 mg), and triethylamine (0.122 mL) were added to an N,N-dimethyl formamide solution (3.0 mL) of [8-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-7-(2-chlorobenzyl)-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-1-yl]acetic acid (179 mg), and the reaction solution was stirred over night. Water and sodium bicarbonate were added to the reaction solution, the solution was rendered alkaline, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated at reduced pressure. The resulting residue was separated and purified by column layer chromatography (silica gel, hexane/ethyl acetate = 5/1 to 1/1), giving the titled product (92.6 mg).

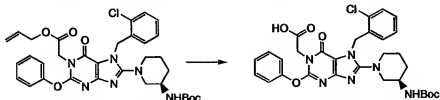
¹H NMR (400 MHz, CDCl₃) δ ppm 7.44–7.39 (m, 3H), 7.26–7.16 (m, 5H), 6.83–6

.78 (m, 1H), 5.55-5.50 (m, 2H), 4.96 (s, 2H), 4.84-4.79 (m, 1H), 4.22 (q, J=7.1Hz, 2H), 3.77-3.72 (m, 1H), 3.42-3.37 (m, 1H), 3.05-3.00 (m, 3H), 1.76-1.50 (m, 4H), 1.40 (s, 9H), 1.26 (t, J=7.1Hz, 3H).

MS (ESI+) 637 (M⁺+1, 73%).

Reference Example 42

[8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-1-yl]acetic acid



Tetrakis triphenylphosphinopalladium (18 mg) and morpholine (0.0532 mL) were added at 0°C to a tetrahydrofuran solution (5.0 mL) of allyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-1-yl]acetate (330 mg), and the reaction solution was stirred for 1 hour at 0°C. Water and citric acid were added to the reaction solution, rendering the solution weakly acidic, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated at reduced pressure. The resulting residue was separated and purified by column layer chromatography (silica gel, chloroform/methanol = 100/1 to 100/3), giving the titled product (37.2 mg).

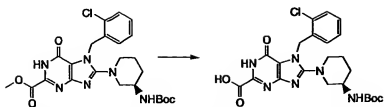
¹H NMR (400 MHz, CDCl₃) δ ppm 7.42-7.37 (m, 3H), 7.26-7.16 (m, 5H), 6.79 (d, J=6.7Hz, 1H), 5.53-5.48 (m, 2H), 4.99 (s, 2H), 4.84-4.79 (m, 1H), 3.77-3.72 (m, 1H), 3.42-3.37 (m, 1H), 3.02-2.97 (m, 3H), 1.74-1.50 (m, 4H), 1.39 (s, 9H).

MS (ESI+) 609 (M⁺+1, 70%).

Reference Example 43

[8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-6,7-dihydro-1H-purine-2-carboxylic acid

286

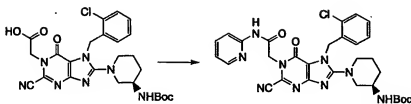


A 1N sodium hydroxide aqueous solution (0.379 mL) was gradually added in the form of drops to a tetrahydrofuran (4 mL) and methanol (6 mL) solution of methyl 8-((3R)-3-((tert-butoxycarbonyl)amino)piperidin-1-yl)-7-(2-chlorobenzyl)-6-oxo-6,7-dihydro-1H-purin-2-carboxylate (98 mg), and the contents were stirred over night at 25°C. The reaction solvent was distilled off at reduced pressure, 10% citric acid aqueous solution (50 mL) was then added, and the solution was extracted twice with chloroform (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated at reduced pressure, giving the titled product (98 mg).

MS (ESI+) 503 ($M^+ + 1$, 28%) .

Reference Example 44

Tert-butyl((3R)-1-[7-(2-chlorobenzyl)-2-amino-6-oxo-1-[2-oxo-2-(pyridine-2-ylamino)ethyl]-6,7-dihydro-1H-purin-8-yl]piperidine-3-yl) carbamate



2-aminipyridine (16.6 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (33.8 mg), 1-hydroxybenzotriazole (23.8 mg), and triethylamine (0.0244 mL) were added to an N,N-dimethyl formamide solution (1.0 mL) of [8-((3R)-3-((tert-butoxycarbonyl)amino)piperidin-1-yl)-7-(2-chlorobenzyl)-2-cyano-6-oxo-6,7-dihydro-1H-purine-1-yl]acetic acid (47.8 mg), and the reaction solution was stirred over night. Water and sodium bicarbonate were added to the reaction solution, the solution was rendered alkaline, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated at reduced pressure. The resulting residue was separated and purified by column layer chromatography (silica gel, chloroform/ethyl acetate = 1/2), giving the

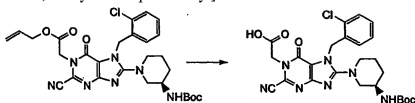
titled product (4.9 mg).

^1H NMR (400 MHz, CDCl_3) δ ppm 8.98 (br, 1H), 8.26 (d, $J=0.9\text{Hz}$, 1H), 7.73–7.68 (m, 2H), 7.38 (d, $J=7.8\text{Hz}$, 1H), 7.24–7.19 (m, 2H), 7.10–7.05 (m, 1H), 6.78 (d, $J=7.0\text{Hz}$, 1H), 5.62–5.57 (m, 2H), 5.07 (s, 2H), 4.78–4.73 (m, 1H), 3.80–3.75 (m, 1H), 3.57–3.52 (m, 1H), 3.28–3.23 (m, 1H), 3.12–3.07 (m, 2H), 2.04–1.50 (m, 4H), 1.41 (s, 9H).

MS (ESI+) 618 ($M^+ + 1$, 37%).

Reference Example 45

[8-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-7-(2-chlorobenzyl)-2-cyano-6-oxo-6,7-dihydro-1H-purine-2-yl]acetic acid



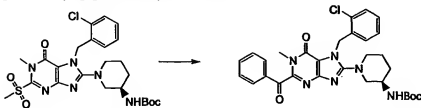
Tetrakis triphenylphosphinopalladium (18 mg) and morpholine (0.0532 mL) were added at 0°C to a tetrahydrofuran solution (1.4 mL) of allyl [8-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-7-(2-chlorobenzyl)-2-cyano-6-oxo-6,7-dihydro-1H-purine-1-yl]acetate (166 mg), and the reaction solution was stirred for 1 hour at 0°C . Water and citric acid were added to the reaction solution, rendering the solution weakly acidic, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated at reduced pressure. The resulting residue was separated and purified by column layer chromatography (silica gel, chloroform/methanol = 100/1 to 100/3), giving the titled product (145 mg).

^1H NMR (400 MHz, CDCl_3) δ ppm 7.44–7.39 (m, 1H), 7.25–7.20 (m, 2H), 6.81–6.76 (m, 1H), 5.59–5.54 (m, 2H), 5.00 (s, 2H), 4.78–4.73 (m, 1H), 3.78–3.73 (m, 1H), 3.42–3.37 (m, 1H), 3.04–2.97 (m, 3H), 1.81–1.56 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 542 ($M^+ + 1$, 53%).

Reference Example 46

Tert-butyl{(3R)-1-[2-benzoyl-7-(2-chlorobenzyl)-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



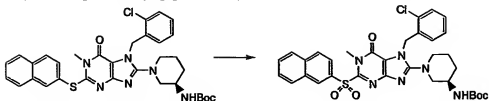
60% sodium hydride dispersion (64 mg) was added to an N,N-dimethyl formamide solution (15 mL) of mandelonitrile (286 mg), and the contents were stirred for 1 hour at 80°C. The reaction solution was cooled to 25°C, an N,N-dimethyl formamide solution (5 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (220 mg) was added in the form of drops, and the ingredients were stirred for 2 hours at 80°C. Saturated sodium bicarbonate aqueous solution (50 mL) was added to the reaction solution, which was extracted 3 times with chloroform (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 10/1 to 1/1), giving the titled product (33 mg).

¹H NMR (300 MHz, CDCl₃) δ ppm 8.03–8.00 (m, 2H), 7.71–7.42 (m, 4H), 7.26–7.23 (m, 2H), 6.86–6.84 (m, 1H), 5.65–5.55 (m, 2H), 5.14–5.12 (m, 1H), 3.69–3.67 (m, 1H), 3.51 (s, 3H), 3.46–3.39 (m, 1H), 3.17–3.05 (m, 3H), 1.83–1.42 (m, 4H), 1.41 (s, 9H).

MS (ESI+) 577 (M⁺+1, 35%).

Reference Example 47

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(naphthylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



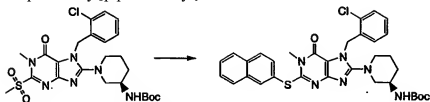
An aqueous solution (1 mL) of sodium tungstate (114 mg) was added while cooled on

ice to a methanol solution (2 mL) and an acetic acid solution (10 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (170 mg), a 30% hydrogen peroxide aqueous solution (0.399 mL) was then gradually added in the form of drops, after 30 minutes the temperature was increased to 25°C, and the ingredients were stirred for 6 hours. The reaction solution was distilled off at reduced pressure, and toluene (30 mL) was added before distillation at reduced pressure (repeated 3 times). Saturated sodium bicarbonate aqueous solution (30 mL) was added, followed by extraction twice with chloroform (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 5/1 to 1/1), giving the titled product (37 mg).

MS (ESI+) 663 ($M^+ + 1$, 24%) ↓

Reference Example 48

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(2-naphthylthio)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate

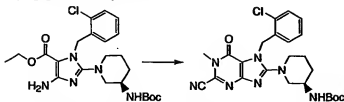


60% sodium hydride dispersion (80 mg) was added to a tetrahydrofuran solution (20 mL) of 2-naphthyl thiol (400 mg), and the ingredients were stirred for 1 hour at 25°C. A tetrahydrofuran solution (10 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (275 mg) was added in the form of drops to the reaction solution, and the ingredients were stirred for 3 hours at 25°C. A 10% potassium carbonate aqueous solution (50 mL) was added to the reaction solution, and the tetrahydrofuran was distilled off at reduced pressure before extraction 3 times with chloroform (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, chloroform/methanol = 100/1 to 20/1), giving the titled product (265 mg).

MS (ESI+) 631 ($M^+ + 1$, 77%) ↓

Reference Example 49

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-2-cyano-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



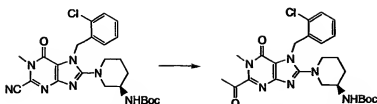
A dichloromethane solution (10 mL) of ethyl 4-amino-2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylate (304 mg) was added to a dichloromethane solution (10 mL) of 4,5-dichloro-1,2,3-dithiazolium chloride (663 mg), a dichloromethane solution (2 mL) of pyridine (0.512 mL) was added in the form of drops, and the ingredients were stirred for 6 hours at 25°C. Tetrahydrofuran (20 mL) was added to the reaction solution, followed by filtration with celite and concentration of the filtrate at reduced pressure. A tetrahydrofuran solution (20 mL) of the reaction mixture was cooled to 0°C, 2N methylamine/tetrahydrofuran solution (15 mL) was gradually added in the form of drops, the temperature was gradually increased to 25°C, and the contents were stirred over night. The tetrahydrofuran was distilled off at reduced pressure, 10% potassium carbonate aqueous solution (50 mL) was then added to the reaction solution, and the solution was extracted 3 times with chloroform (40 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 10/1 to 1/1), giving the titled product (199 mg).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42 (d, J=7.5 Hz, 1H), 7.25–7.16 (m, 2H), 6.72 (d, J=7.3 Hz, 1H), 5.64 (d, J=17.4 Hz, 1H), 5.55 (d, J=17.4 Hz, 1H), 4.70–4.68 (m, 1H), 3.78 (s, 3H), 3.53–3.49 (m, 1H), 3.38–3.34 (m, 1H), 3.24–3.22 (m, 1H), 3.09–2.99 (m, 2H), 1.80–1.48 (m, 4H), 1.41 (s, 9H).
MS (ESI+) 498 (M⁺+1, 100%).

Reference Example 50

Tert-butyl{(3R)-1-[2-(2-chlorobenzyl)-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate

291



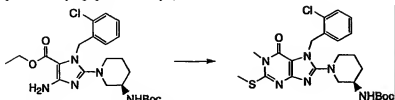
A tetrahydrofuran solution (5 mL) of methyl magnesium bromide/3M tetrahydrofuran solution (0.088 mL) was cooled to -78°C , copper bromide (6 mg), tert-butyl dimethylsilyl chloride (29 mg), and tetrahydrofuran solution (10 mL) of tert-butyl[(3R)-1-[7-(2-chlorobenzyl)-2-cyano-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate (44 g) were added, the ingredients were stirred for 1 hour, and the temperature was gradually increased to 25°C over a period of 3 hours and the contents were stirred. The reaction solution was cooled to 0°C , methyl magnesium bromide/3M tetrahydrofuran solution (0.750 mL) was added in the form of drops, the ingredients were stirred for 30 minutes, the temperature was then increased to 25°C , and the ingredients were stirred for 5 hours. Saturated ammonium chloride aqueous solution (50 mL) was added to the reaction solution, and the tetrahydrofuran was distilled off at reduced pressure before extraction with ethyl acetate (100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 1/1), giving the titled product (12 mg).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.43–7.40 (m, 1H), 7.24–7.16 (m, 2H), 6.75 (d, $J=7.1\text{ Hz}$, 1H), 5.68 (d, $J=16.8\text{ Hz}$, 1H), 5.57 (d, $J=16.8\text{ Hz}$, 1H), 4.71–4.69 (m, 1H), 3.78–3.76 (m, 1H), 3.70 (s, 3H), 3.52–3.47 (m, 1H), 3.15–3.00 (m, 3H), 2.77 (s, 3H), 1.79–1.48 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 515 ($M^+ + 1$, 17%).

Reference Example 51

Tert-butyl[(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylthio)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate



Methyl isothiocyanate (1.11 g) was added to a pyridine solution (30 mL) of ethyl 4-

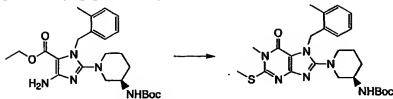
amino-2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylate (36.4 mg) in a nitrogen atmosphere, and the ingredients were heated and stirred for 6 hours at 125°C. The reaction solution was cooled to 25°C, potassium carbonate (2.10 g) was added, the temperature was again increased to 125°C, and the ingredients were heated and stirred for 6 hours. The reaction solution was cooled to 25°C and filtered, and toluene (30 mL) was added to the filtrate before concentration at reduced pressure (repeated 4 times). Potassium carbonate (2.10 g) was added to a tetrahydrofuran solution (30 mL) of the reaction solution, it was cooled to 0°C, methyl iodide (0.948 mL) was added in the form of drops, the temperature was then increased to 25°C, and the ingredients were stirred for 4 hours. Toluene (50 mL) was added to the reaction solution before concentration at reduced pressure (repeated 4 times). Water (100 mL) was added to the reaction mixture, and it was extracted 3 times with chloroform (100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 5/1 to 1/1), giving the titled product (4.20 mg).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.41–7.38 (m, 1H), 7.23–7.14 (m, 2H), 6.75 (d, J=7.1Hz, 1H), 5.60 (d, J=17.1Hz, 1H), 5.50 (d, J=17.1Hz, 1H), 4.78–4.76 (m, 1H), 3.77–3.75 (m, 1H), 3.53 (s, 3H), 3.47–3.41 (m, 1H), 3.06–3.00 (m, 3H), 2.67 (s, 3H), 1.72–1.44 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 519 (M⁺+1, 100%) .

Reference Example 128

Tert-butyl{(3R)-1-[7-(2-methylbenzyl)-1-methyl-2-(methylthio)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



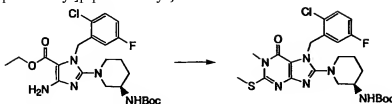
The compound of Reference Example 128 was synthesized in the same manner as in Reference Example 51.

MS (ESI+) 499 (M⁺+1, 86%) .

Reference Example 129

Tert-butyl{(3R)-1-[7-(2-chloro-5-fluorobenzyl)-1-methyl-2-(methylthio)-6-oxo-6,7-dihydro-1H-

purine-8-yl]piperidin-3-yl}carbamate



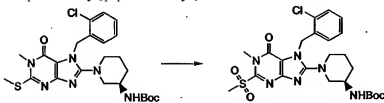
The compound of Reference Example 129 was synthesized in the same manner as in Reference Example 51.

^1H NMR (400MHz, CDCl_3) δ ppm 7.35 (dd, $J=5.0, 8.8\text{Hz}$, 1H), 6.92 (dt, $J=3.0, 8.4\text{Hz}$, 1H), 6.50–6.47 (m, 1H), 5.54–5.43 (m, 2H), 4.78–4.76 (m, 1H), 3.79–3.71 (m, 1H), 3.52 (s, 3H), 3.45 (dd, $J=3.3, 12.2\text{Hz}$, 1H), 3.15–3.14 (m, 1H), 3.03–2.95 (m, 2H), 2.68 (s, 3H), 1.83–1.57 (m, 3H), 1.55–1.53 (m, 1H), 1.41 (s, 9H).

MS (ESI+) 537 ($M^+ + 1$, 88%) .

Reference Example 52

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



The compound of Reference Example 52 was synthesized in the same manner as in Reference Example 47.

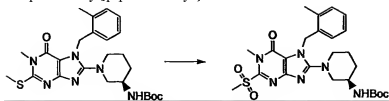
^1H NMR (300 MHz, CDCl_3) δ ppm 7.44–7.41 (m, 1H), 7.26–7.18 (m, 2H), 6.75 (d, $J=7.1\text{Hz}$, 1H), 5.66 (d, $J=17.0\text{Hz}$, 1H), 5.55 (d, $J=17.0\text{Hz}$, 1H), 4.69–4.67 (m, 1H), 3.89 (s, 3H), 3.77–3.75 (m, 1H), 3.56 (s, 3H), 3.50–3.48 (m, 1H), 3.18–3.16 (m, 1H), 3.07–2.97 (m, 2H), 1.84–1.66 (m, 3H), 1.52–1.48 (m, 1H), 1.42 (s, 9H).

MS (ESI+) 551 ($M^+ + 1$, 100%) .

Reference Example 130

Tert-butyl{(3R)-1-[7-(2-methylbenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-

1H-purine-8-yl]piperidin-3-yl}carbamate

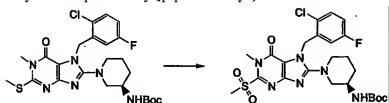


The compound of Reference Example 130 was synthesized in the same manner as in Reference Example 47.

MS (ESI+) 531 ($M^+ + 1$, 66%) .

Reference Example 131

Tert-butyl{(3R)-1-[7-(2-chloro-5-fluorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



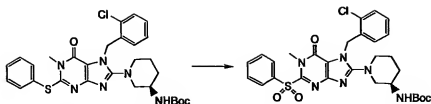
The compound of Reference Example 131 was synthesized in the same manner as in Reference Example 47.

^1H NMR (400MHz, CDCl_3) δ ppm 7.38 (dd, $J=5.0, 8.8\text{Hz}$, 1H), 6.96 (dt, $J=3.6, 6.6\text{Hz}$, 1H), 6.49–6.47 (m, 1H), 5.60–5.48 (m, 2H), 4.69–4.67 (m, 1H), 3.89 (s, 3H), 3.79–3.74 (m, 1H), 3.56 (s, 3H), 3.54–3.52 (m, 1H), 3.25–3.20 (m, 1H), 3.07–2.93 (m, 2H), 1.88–1.85 (m, 1H), 1.76–1.74 (m, 2H), 1.57–1.54 (m, 1H), 1.40 (s, 9H).

MS (ESI+) 569 ($M^+ + 1$, 37%) .

Reference Example 53

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-(phenylsulfonyl)-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate

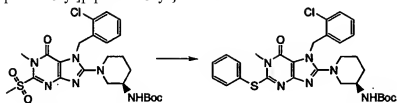


The compound of Reference Example 53 was synthesized in the same manner as in Reference Example 47.

¹H NMR (300 MHz, CDCl₃) δ ppm 8.06–8.03 (m, 2H), 7.77–7.72 (m, 1H), 7.65–7.59 (m, 2H), 7.41 (d, J=6.4Hz, 1H), 7.24–7.16 (m, 2H), 6.68 (d, J=7.5Hz, 1H), 5.64 (d, J=16.8Hz, 1H), 5.53 (d, J=16.8Hz, 1H), 4.67–4.65 (m, 1H), 4.04 (s, 3H), 3.71–3.69 (m, 1H), 3.41–3.38 (m, 1H), 3.02–2.94 (m, 3H), 1.76–1.43 (m, 4H), 1.39 (s, 9H).

Reference Example 54

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-(phenylthio)-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate



60% sodium hydride dispersion (80 mg) was added to a tetrahydrofuran solution (20 mL) of thiophenol (275 mg), and the contents were stirred for 1 hour at 25°C. A tetrahydrofuran solution (10 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate (3.85 g) was added in the form of drops to the reaction solution, and the solution was stirred for 3 hours at 25°C. 10% potassium carbonate aqueous solution (50 mL) was added to the reaction solution, and the tetrahydrofuran was distilled off at reduced pressure before extraction 3 times with chloroform (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, chloroform/methanol = 100/1 to 20/1), giving the titled product (262 mg).

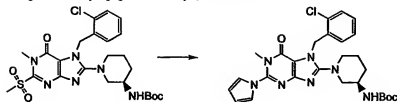
¹H NMR (300 MHz, CDCl₃) δ ppm 7.64–7.64 (m, 2H), 7.46–7.38 (m, 4H), 7.23–7.12 (m, 2H), 6.69 (d, J=6.0Hz, 1H), 5.59 (d, J=17.1Hz, 1H), 5.49 (d, J=17.

1Hz, 1H), 4.75–4.73 (m, 1H), 3.71–3.69 (m, 1H), 3.66 (s, 3H), 3.36–3.32 (m, 1H), 3.01–2.97 (m, 3H), 1.70–1.40 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 581 ($M^+ + 1$, 28%).

Reference Example 55

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-(1H-pyrrol-1-yl)-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate



60% sodium hydride dispersion (32 mg) was added to a tetrahydrofuran solution (5 mL) of pyrrole (67 mg), and the contents were stirred for 1 hour at 60°C. The reaction solution was cooled to 25°C, a tetrahydrofuran solution (2 mL) of tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-2-(methanesulfonyl)-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl}carbamate (110 mg) was added in the form of drops to the reaction solution, and the solution was stirred for 4 hours at 25°C. Saturated ammonium chloride aqueous solution (50 mL) was added to the reaction solution, and the tetrahydrofuran was distilled off at reduced pressure before extraction 3 times with chloroform (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 5/1 to 1/2), giving the titled product (89 mg).

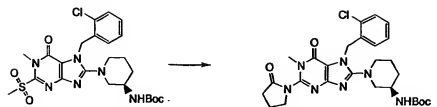
^1H NMR (300 MHz, CDCl_3) δ ppm 7.43–7.40 (m, 1H), 7.24–7.18 (m, 2H), 7.09 (t, $J=2.2\text{ Hz}$, 2H), 6.82 (d, $J=6.8\text{ Hz}$, 1H), 6.35 (d, $J=2.2\text{ Hz}$, 2H), 5.64 (d, $J=17.0\text{ Hz}$, 1H), 5.54 (d, $J=17.0\text{ Hz}$, 1H), 4.76–4.74 (m, 1H), 3.77–3.75 (m, 1H), 3.50 (s, 3H), 3.45–3.42 (m, 1H), 3.15–3.02 (m, 3H), 1.77–1.42 (m, 4H), 1.41 (s, 9H).

MS (ESI+) 538 ($M^+ + 1$, 100%).

Reference Example 56

Tert-butyl{(3R)-1-[7-(2-chlorobenzyl)-1-methyl-6-oxo-2-(2-oxopyrrolidin-1-yl)-6,7-

dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate

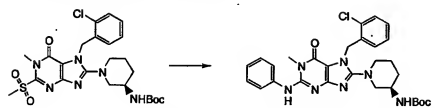


The compound of Reference Example 56 was synthesized in the same manner as in Reference Example 55.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.42–7.39 (m, 1H), 7.23–7.17 (m, 2H), 6.81–6.78 (m, 1H), 5.63 (d, J=17.0Hz, 1H), 5.52 (d, J=17.0Hz, 1H), 4.75–4.73 (m, 1H), 3.78–3.76 (m, 1H), 3.53 (s, 3H), 3.46–3.42 (m, 1H), 3.08–3.00 (m, 3H), 2.61–2.56 (m, 2H), 2.30–2.17 (m, 2H), 1.75–1.42 (m, 6H), 1.41 (s, 9H). MS (ESI+) 556 (M⁺+1, 19%) .

Reference Example 132

Tert-butyl{[(3R)-1-[7-(2-chlorobenzyl)-2-phenylamino-1-methyl-6-oxo-6,7-dihydro-1H-purine-8-yl]piperidin-3-yl]carbamate

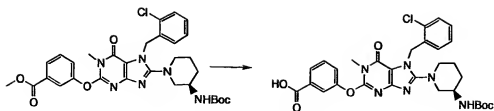


The compound of Reference Example 132 was synthesized in the same manner as in Reference Example 55.

MS (ESI+) 564 (M⁺+1, 73%) .

Reference Example 58

3-[[8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-6-oxo-6,7-dihydro-1H-purine-2-yl]oxy]benzoic acid

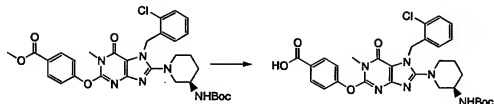


The compound of Reference Example 58 was synthesized in the same manner as in Reference Example 43.

MS (ESI+) 609 ($M^+ + 1$, 56%) .

Reference Example 133

4-[[8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-1-methyl-6-oxo-6,7-dihydro-1H-purine-2-yl]oxy]benzoic acid

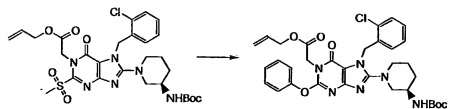


The compound of Reference Example 133 was synthesized in the same manner as in Reference Example 43.

MS (ESI+) 609 ($M^+ + 1$, 75%) .

Reference Example 67

Allyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-2-phenoxy-6,7-dihydro-1H-purine-1-yl]acetate



The compound of Reference Example 67 was synthesized in the same manner as in Reference Example 31.

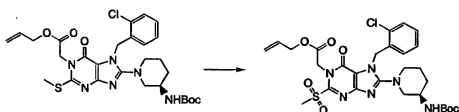
^1H NMR (400 MHz, CDCl_3) δ ppm 7.41–7.37 (m, 3H), 7.26–7.17 (m, 5H), 6.78 (d, $J=7.0$, 1H), 5.88–5.85 (m, 1H), 5.55–5.46 (m, 2H), 5.33–5.21 (m, 2H), 5.00 (s, 2H), 4.79–4.59 (m, 1H), 4.68–4.11 (m, 2H), 3.76–3.68 (m, 1H), 3.37

(dd, $J=3.2, 12.5$ Hz, 1H), 3.05–2.96 (m, 3H), 1.75–1.50 (m, 4H), 1.40 (s, 9H).

MS (ESI+) 649 ($M^+ + 1$, 30%).

Reference Example 68

Allyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-1-yl]acetate



The compound of Reference Example 68 was synthesized in the same manner as in Reference Example 47.

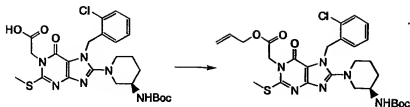
Oxone (4.65 g, Aldrich) was added to a methanol-water suspension (25 mL) of 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-4(5H)-one (380 mg), and the mixture was vigorously stirred over night at room temperature. Saturated sodium bicarbonate aqueous solution was added to the reaction solution, rendering it neutral, water was added to the residue obtained by concentration at reduced pressure, and it was extracted 3 times with chloroform. The pooled organic layers were washed with saturated brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated at reduced pressure. The resulting crude product (440 mg) was used as such in subsequent reaction.

^1H NMR (400 MHz, CDCl_3) δ ppm 7.40 (dd, $J=7.8, 1.5$ Hz, 1H), 7.27–7.22 (m, 2H), 6.81–6.76 (m, 1H), 5.93–5.88 (m, 1H), 5.65–5.60 (m, 1H), 5.31 (dd, $J=1.4, 17.2$ Hz, 2H), 5.28–5.23 (m, 2H), 4.73–4.67 (m, 1H), 4.70–4.65 (m, 2H), 3.81–3.76 (m, 1H), 3.55 (s, 3H), 3.19–3.14 (m, 1H), 3.08–3.03 (m, 2H), 1.74–1.69 (m, 1H), 1.61–1.51 (m, 3H), 1.40 (s, 9H).

MS (ESI+) 635 ($M^+ + 1$, 36%).

Reference Example 69

2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-4(5H)-one



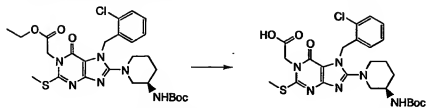
Potassium carbonate (828 mg) and 3-bromopropene (0.312 mL) were added to an N,N-dimethyl formamide-chloroform suspension (5 mL + 5 mL) of [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-(methylthio)-6-oxo-6,7-dihydro-1H-purine-1-yl]acetic acid (563 mg), and the reaction solution was stirred for 4 hours at room temperature. Water was added to the reaction solution, the solution was rendered alkaline, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, chloroform/ethyl acetate = 20/1 to 4/1), giving the titled product (490 mg).

¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (dd, J=1.5, 7.8Hz, 1H), 7.23-7.18 (m, 2 H), 6.81-6.76 (m, 1H), 5.93-5.88 (m, 1H), 5.56-5.51 (m, 2H), 5.30 (dd, J=1.4, 17.2Hz, 1H), 5.23 (d, J=10.4Hz, 1H), 4.90 (s, 2H), 4.80-4.75 (m, 1H), 4.69-4.64 (m, 2H), 3.82-3.77 (m, 1H), 3.49-3.44 (m, 1H), 3.10-3.05 (m, 3H), 2.68 (s, 3H), 1.83-1.78 (m, 1H), 1.61-1.51 (m, 3H), 1.42 (s, 9H).

MS (ESI⁺) 603 (M⁺+1, 99%).

Reference Example 70

[8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-(methylthio)-6-oxo-6,7-dihydro-1H-purine-1-yl]acetic acid



Lithium hydroxide aqueous solution (1 N, 11 mL) was added to a tetrahydrofuran-ethanol mixture (11 mL + 5.0 mL) of ethyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-(methylthio)-6-oxo-6,7-dihydro-1H-purine-1-yl]acetate (650 mg), and the reaction solution was heated and

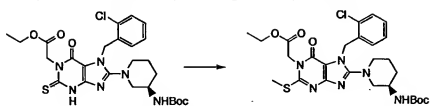
stirred for 10 minutes at 60°C. The reaction solution was allowed to cool to room temperature and concentrated at reduced pressure, water and citric acid were added to the resulting residue, rendering the solution weakly acidic, and it was extracted twice with chloroform. The pooled organic layers were washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting crude product (740 mg) was used as such in subsequent reaction.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.37 (d, J=7.5 Hz, 1H), 7.22-7.17 (m, 2H), 6.77 (d, J=7.4 Hz, 1H), 5.57-5.52 (m, 2H), 4.87 (s, 2H), 4.85-4.80 (m, 1H), 3.79-3.74 (m, 1H), 3.49-3.42 (m, 1H), 3.11-3.06 (m, 3H), 2.66 (s, 3H), 1.81-1.76 (m, 1H), 1.75-1.48 (m, 3H), 1.41 (s, 9H).

MS (ESI+) 563 (M⁺+1, 90%).

Reference Example 71

Ethyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-(methylthio)-6-oxo-6,7-dihydro-1H-purine-1-yl]acetate



Potassium carbonate (489 mg) and methyl iodide (0.110 mL) were added to an acetonitrile solution (27 mL) of ethyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-2-thiooxo-2,3,6,7-tetrahydro-1H-purine-1-yl]acetate (1.07 g), and the solution was stirred for 2 hours at room temperature. The reaction solution was concentrated at reduced pressure, water was added to the residue, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, chloroform/ethyl acetate = 10/1 to 5/1), giving the titled product (0.690 g).

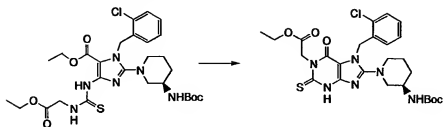
¹H NMR (400 MHz, CDCl₃) δ ppm 7.44-7.39 (m, 1H), 7.21-7.16 (m, 2H), 6.81-6.76 (m, 1H), 5.58-5.53 (m, 2H), 4.86 (s, 2H), 4.82-4.77 (m, 1H), 4.26-4.21 (m, 2H), 3.82-3.77 (m, 1H), 3.48-3.43 (m, 1H), 3.12-3.07 (m, 3H), 2.68 (s, 3H), 1.82-1.77 (m, 1H), 1.67-1.51 (m, 3H), 1.42 (s, 9H), 1.30-1.25 (m, 3

H).

MS (ESI+) 591 ($M^+ + 1$, 84%) .

Reference Example 72

Ethyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-6-oxo-2-thioxo-2,3,6,7-tetrahydro-1H-purine-1-yl]acetate



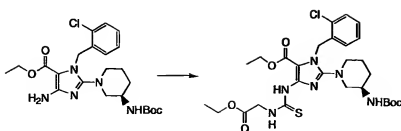
Sodium (625 mg) was added to ethanol (120 mL), and 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (15.4 g) was added to the resulting sodium ethoxide solution at room temperature. The reaction solution was stirred for 30 minutes at room temperature, and saturated ammonium chloride aqueous solution (5 mL) was added. Water and citric acid were added to the reaction solution, rendering the solution weakly acidic, and it was extracted twice with ethyl acetate. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure, giving the titled crude product (15.4 g).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.45–7.40 (m, 1H), 7.28–7.23 (m, 2H), 6.97–6.92 (m, 1H), 5.52–5.47 (m, 2H), 5.19 (s, 2H), 4.68–4.63 (m, 1H), 4.20 (q, $J=7.1$ Hz, 2H), 3.81–3.76 (m, 1H), 3.72–3.67 (m, 1H), 3.30–3.25 (m, 3H), 1.88–1.83 (m, 1H), 1.66–1.61 (m, 2H), 1.53–1.48 (m, 1H), 1.41 (s, 9H), 1.26 (t, $J=7.1$ Hz, 3H).

MS (ESI+) 577 ($M^+ + 1$, 54%) .

Reference Example 73

2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one



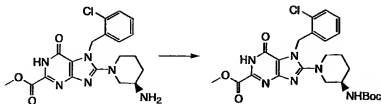
Ethyl isothiocyanatoacetate (10.0 g) was added at room temperature to an ethanol solution (62 mL) of ethyl 4-amino-2-((3R)-3-((tert-butoxycarbonyl)amino)piperidin-1-yl)-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylate (14.8 g), and the ingredients were heated and stirred for 3 hours. The reaction solution was cooled to room temperature and concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, hexane/ethyl acetate = 5/1 to 1/1), giving the titled product (15.4 g).

¹H NMR (400 MHz, CDCl₃) δ ppm 10.9 (s, 1H), 9.50 (brs, 1H), 7.44–7.39 (m, 1H), 7.25–7.20 (m, 2H), 6.72–6.67 (m, 1H), 5.34 (s, 2H), 4.65–4.55 (m, 3H), 4.25 (q, J=7.1 Hz, 2H), 4.20–4.15 (m, 2H), 3.90–3.85 (m, 1H), 3.11–2.91 (m, 3H), 1.94–1.89 (m, 1H), 1.61–1.48 (m, 3H), 1.41 (s, 9H), 1.31 (t, J=7.1 Hz, 3H), 1.20–1.15 (m, 3H).

MS (ESI⁺) 623 (M⁺, 100%).

Reference Example 74

Methyl 8-((3R)-3-((tert-butoxycarbonyl)amino)piperidin-1-yl)-7-(2-chlorobenzyl)-6-oxo-6,7-dihydro-1H-purinee-2-carboxylate



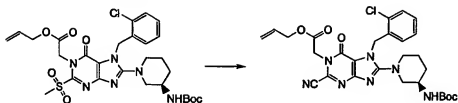
Water (5 mL) and saturated sodium bicarbonate aqueous solution (5 mL) were added to a tetrahydrofuran (10 mL) solution of methyl 8-((3R)-3-aminopiperidin-1-yl)-7-(2-chlorobenzyl)-6-oxo-6,7-dihydro-1H-purinee-2-carboxylate (367 mg) [sic], di-tert-butyl dicarbonate (192 mg) was added, and the ingredients were stirred for 4 hours at 25°C. The reaction solution was concentrated at reduced pressure, ethyl acetate (150 mL)

was added, and the solution was washed with water and saturated sodium chloride aqueous solution. The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography (silica gel, chloroform/methanol = 100/1 to 30/1), giving the titled product (102 mg).

MS (ESI+) 517 ($M^+ + 1$, 19%) .

Reference Example 75

Allyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-cyano-6-oxo-6,7-dihydro-1H-purine-1-yl]acetate



Sodium cyanide (36.3 mg) was added to an N,N-dimethyl formamide (3.6 mL) solution of allyl [8-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-7-(2-chlorobenzyl)-2-(methylsulfonyl)-6-oxo-6,7-dihydro-1H-purine-1-yl]acetate (505 mg) at 0°C. The reaction solution was stirred for 2 hours at room temperature, water and sodium bicarbonate aqueous solution were added, rendering the solution alkaline, and it was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, chloroform/ethyl acetate = 1/0 to 10/1), giving the titled product (245 mg).

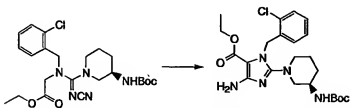
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.44–7.39 (m, 1H), 7.25–7.20 (m, 2H), 6.80–6.75 (m, 1H), 5.94–5.89 (m, 1H), 5.63–5.58 (m, 2H), 5.36–5.31 (m, 2H), 5.02 (s, 2H), 4.75–4.70 (m, 3H), 3.80–3.75 (m, 1H), 3.57–3.52 (m, 1H), 3.30–3.25 (m, 1H), 3.10–3.05 (m, 2H), 1.89–1.84 (m, 1H), 1.71–1.56 (m, 3H), 1.41 (s, 9H).

MS (ESI+) 582 ($M^+ + 1$, 100%) .

Reference Example 76

Ethyl 4-amino-2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-1-(2-

chlorobenzyl)-1H-imidazole-5-carboxylate



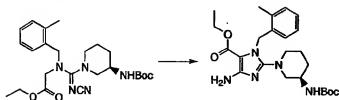
Sodium hydride (60%, 2.01 g) was added to tetrahydrofuran (233 mL) at room temperature, and the mixture was stirred for 30 minutes. A tetrahydrofuran solution (100 mL) of ethyl N-[(Z)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino)methyl]-N-(2-chlorobenzyl)glycinate (16.0 g) was added at 0°C to the reaction solution, and the mixture was stirred for 2 hours at room temperature. The reaction solution was cooled to 0°C, water (1.8 mL) was carefully added, and saturated ammonium chloride aqueous solution (10 mL) was then added. The reaction solution was concentrated at reduced pressure, water and potassium carbonate were added to the residue, rendering the solution alkaline, and it was extracted twice with ethyl acetate. The pooled organic layers were dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated at reduced pressure, giving the titled crude product (16.7 g).

¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (dd, J=1.6, 7.7 Hz, 1H), 7.23-7.18 (m, 2H), 6.81-6.76 (m, 1H), 5.31 (s, 2H), 5.23-5.03 (m, 1H), 4.12 (q, J=7.1 Hz, 2H), 3.82-3.77 (m, 1H), 3.38-3.33 (m, 1H), 3.05-3.00 (m, 3H), 1.80-1.75 (m, 2H), 1.62-1.57 (m, 2H), 1.41 (s, 9H), 1.02 (t, J=7.1 Hz, 3H).

MS (ESI⁺) 478 (M⁺+1, 100%)

Reference Example 134

Ethyl 4-amino-2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-1-(2-methylbenzyl)-1H-imidazole-5-carboxylate



The compound of Reference Example 134 was synthesized in the same manner as in Reference Example 76.

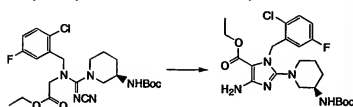
¹H NMR (400 MHz, CDCl₃) δ ppm 7.15-7.05 (m, 3H), 6.63 (d, J=7.3 Hz, 1H), 5.17-5.10 (m, 2H), 4.98-4.96 (m, 3H), 4.08-4.06 (m, 2H), 3.76-3.73 (m, 1H), 3.2

9-3.25 (m, 1H), 2.97-2.86 (m, 3H), 2.33 (s, 3H), 1.85-1.49 (m, 4H), 1.41 (s, 9H), 1.07-1.01 (m, 3H).

MS (ESI+) 458 (M⁺+1, 100%)

Reference Example 135

Ethyl 4-amino-2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-1-(2-methylbenzyl)-1H-imidazole-5-carboxylate



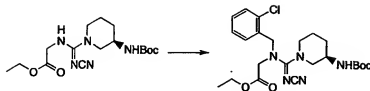
The compound of Reference Example 135 was synthesized in the same manner as in Reference Example 76.

¹H NMR (400MHz, CDCl₃) δ ppm 7.33 (dd, J=5.0, 8.7Hz, 1H), 6.90 (dt, J=3.0, 8.4Hz, 1H), 6.54-6.52 (m, 1H), 5.21 (s, 2H), 5.02-4.96 (m, 3H), 4.14-4.10 (m, 2H), 3.79-3.71 (m, 1H), 3.28 (dd, J=3.2, 12.1Hz, 1H), 2.96-2.82 (m, 3H), 1.79-1.51 (m, 4H), 1.41 (s, 9H), 1.10-1.08 (m, 3H).

MS (ESI+) 496 (M⁺+1, 100%)

Reference Example 77

Ethyl N-[(Z)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino)methyl]-N-(2-chlorobenzyl)glycinate



2-chlorobenzyl bromide (18.3 g) and potassium carbonate (24.6 g) were added to an acetonitrile solution (113 mL) of ethyl N-[(E)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino)methyl]glycinate (21.0 g), and the ingredients were stirred for 2 hours at 70°C. After cooling, the reaction solution was filtered and concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, hexane/ethyl acetate = 2/1 to 2/3), giving

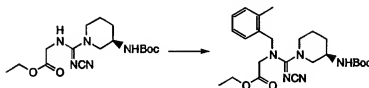
the titled product (16.3 g).

^1H NMR (400 MHz, CDCl_3) δ ppm 7.45–7.40 (m, 1H), 7.34–7.29 (m, 3H), 4.63–4.58 (m, 2H), 4.22 (q, $J=7.1\text{ Hz}$, 2H), 4.03–3.98 (m, 2H), 3.76–3.71 (m, 2H), 3.54–3.25 (m, 4H), 1.95–1.90 (m, 2H), 1.71–1.59 (m, 2H), 1.44 (s, 9H), 1.29 (t, $J=7.1\text{ Hz}$, 3H).

MS (ESI+) 478 ($M^+ + 1$, 82%)

Reference Example 136

Ethyl N-[(Z)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino)methyl]-N-(2-methylbenzyl)glycinate



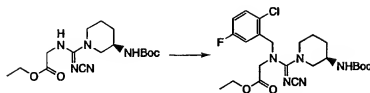
The compound of Reference Example 136 was synthesized in the same manner as in Reference Example 77.

^1H NMR (400 MHz, CDCl_3) δ ppm 7.24–7.18 (m, 3H), 7.13–7.11 (m, 1H), 4.89–4.80 (m, 1H), 4.49 (s, 2H), 4.19 (q, $J=7.1\text{ Hz}$, 2H), 4.02–3.88 (m, 2H), 3.76–3.57 (m, 3H), 3.42–3.40 (m, 1H), 3.25–3.20 (m, 1H), 2.23 (s, 3H), 1.95–1.87 (m, 2H), 1.71–1.61 (m, 2H), 1.43 (s, 9H), 1.27 (t, $J=7.1\text{ Hz}$, 3H).

MS (ESI+) 458 ($M^+ + 1$, 37%)

Reference Example 137

Ethyl N-[(Z)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino)methyl]-N-(2-chloro-5-fluorobenzyl)glycinate



The compound of Reference Example 137 was synthesized in the same manner as in Reference Example 77.

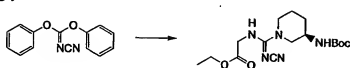
^1H NMR (400 MHz, CDCl_3) δ ppm 7.36 (dd, $J=5.0, 8.8\text{ Hz}$, 1H), 7.08–7.06 (m, 1H),

7.03–6.98 (m, 1H), 4.79–4.74 (m, 1H), 4.62–4.52 (m, 2H), 4.23 (q, $J=7.1$ Hz, 2H), 4.03–3.89 (m, 2H), 3.74–3.59 (m, 3H), 3.42–3.38 (m, 1H), 3.20–3.16 (m, 1H), 1.95–1.71 (m, 2H), 1.70–1.69 (m, 1H), 1.59–1.56 (m, 1H), 1.43 (s, 9H), 1.29 (t, $J=7.1$ Hz, 3H).

MS (ESI+) 496 ($M^+ + 1$, 48%)

Reference Example 78

Ethyl N-[(E)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl} (cyanoimino)methyl] glycinate



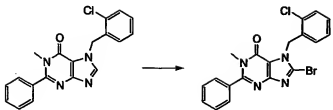
(R)-tert-3-butylpiperidin-3-yl carbamate (73.0 g) was added to a 2-propanol suspension (1.46 L) of diphenyl cyanoimide carbonate (86.8 g), and the reaction solution was stirred for 30 minutes at room temperature. The reaction solution was heated to 50°C, glycine ethyl ester hydrochloride (254 g) and triethylamine (254 mL) were added, and the reaction solution was again heated and stirred for 6 hours at 80°C. The solution was allowed to cool to room temperature, and the precipitate was filtered off and washed with ethyl acetate. The filtrate was concentrated at reduced pressure, and water and potassium carbonate were added to the residue, giving an alkaline solution which was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, hexane/ethyl acetate = 1/1 to 0/1), giving the titled product (133 g) in amorphous form.

^1H NMR (400 MHz, CDCl_3) δ ppm 5.61 (br, 1H), 4.66 (br, 1H), 4.24 (q, $J=7.1$ Hz, 2H), 4.25–4.20 (m, 1H), 3.78–3.37 (m, 5H), 1.98–1.93 (m, 1H), 1.85–1.80 (m, 1H), 1.71–1.66 (m, 2H), 1.45 (s, 9H), 1.30 (t, $J=7.1$ Hz, 3H).

MS (ESI+) 354 ($M^+ + 1$, 20%) .

Reference Example 79

8-bromo-7-(2-chlorobenzyl)-1-methyl-2-phenyl-1,7-dihydro-6H-purine-6-one



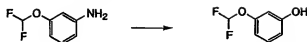
A dimethyl formamide solution (20 mL) of 8-bromo-7-(2-chlorobenzyl)-2-phenyl-1,7-dihydro-6H-purine-6-one (1.00 g) was added to a dimethyl formamide solution (2.4 mL) of sodium hydride (106 mg), and the reaction solution was stirred for 1 hour at room temperature. Methyl iodide (0.180 mL) was added to the reaction solution and stirred over night. Dilute hydrochloric acid was added to the reaction solution, giving an acidic solution, which was extracted twice with chloroform. The pooled organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, chloroform/methanol = 100/1 to 50/1), giving the titled product (1.03 g).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.13–8.08 (m, 2H), 7.65–7.51 (m, 4H), 7.41–7.36 (m, 1H), 7.34–7.29 (m, 1H), 6.66–6.61 (m, 1H), 5.73 (s, 2H), 3.31 (s, 3H).

MS (ESI+) 431 (M⁺+1, 100%)

Reference Example 138

3-difluoromethoxyphenol

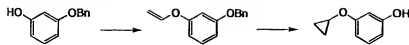


An aqueous solution (20 mL) of sodium sulfite (2.34 g) was added in the form of drops at 0°C to a 15% sulfuric acid aqueous solution of 3-difluoromethoxyaniline (4.90 g), and the contents were stirred for 30 minutes. The product was allowed to return to room temperature and was then heated to 70°C and stirred for 2 hours. The reaction solution was cooled to room temperature, water (100 mL) was added, and the solution was extracted with ethyl acetate (100 mL). The organic layer was washed with saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, hexane/ethyl acetate = 50/1 to 5/1), giving the titled product (2.13 g).

¹H NMR (400 MHz, CDCl₃) δ ppm 7.21 (t, J=8.2Hz, 1H), 6.70–6.62 (m, 3H), 6.49 (t, J_{H-F}=72.5Hz, 1H), 5.40 (br, 1H).

Reference Example 139

3-cyclopropoxyphenol



Cesium carbonate (2.34 g) and 2-chloroethyl-p-toluenesulfonate (9.39 g) were added to a tetrahydrofuran solution (40 mL) of 3-benzyloxyphenol (4.00 g) in a nitrogen atmosphere, and the contents were heated and stirred for 30 hours at 65°C. The reaction solution was cooled to room temperature, the solids were filtered off, and the filtrate was concentrated at reduced pressure. Tert-butoxypotassium (6.73 g) was added to a toluene solution (50 mL) of the crude product, and the mixture was stirred for 1 hour at 110°C. The reaction solution was cooled to room temperature, water (300 mL) was added, and the solution was extracted with ethyl acetate (300 mL). The organic layer was washed with saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated at reduced pressure. The resulting residue was separated and purified by column chromatography (silica gel, hexane/ethyl acetate = 100/1 to 20/1), giving a vinyl ether intermediate (3.44 g).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.44–7.18 (m, 6H), 6.72–6.59 (m, 4H), 5.04 (s, 2H), 4.77 (dd, J=1.6, 13.7Hz, 1H), 4.43 (dd, J=1.6, 6.1Hz, 1H).

A 1,2-dichloroethane solution (12 mL) of diethyl zinc (11.58 mL 1M hexane solution) was cooled to -5°C in a nitrogen atmosphere, a 1,2-dichloroethane solution (5 mL) of trichloroacetic acid (1.89 g) was gradually added in the form of drops, and the contents were stirred for 20 minutes. Diiodomethane (0.93 mL) was also added in the form of drops and stirred for 10 minutes, and a 1,2-dichloroethane solution (5 mL) of the above vinyl ether intermediate (1.31 g) was added in the form of drops. The solution was then gradually returned to room temperature over a period of 2 hours and stirred over night. Then, 2 N hydrochloric acid (20 mL) was added to the reaction solution, the 1,2-dichloroethane was distilled off at reduced pressure, and the material was then diluted with diethyl ether (200 mL). The organic layer was washed with 1N hydrochloric acid, 2.5 N sodium hydroxide aqueous solution and saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated at reduced pressure, and the resulting residue was separated and purified by column chromatography (silica gel, hexane/ethyl acetate = 100/1 to 20/1), giving a benzyl ether (0.74 g) of 3-cyclopropoxyphenol. 10% palladium-carbon catalyst (50% wet) (0.36 g) was added to a tetrahydrofuran (20 mL) and ethanol (20 mL) solution of the resulting

benzyl ether (0.74 g), and the contents were stirred for 5 hours at room temperature in a hydrogen atmosphere. The reaction solution was dried over anhydrous sodium sulfate and filtered with celite, and the filtrate was concentrated at reduced pressure, giving the titled 3-cyclopropoxyphenol (0.51 g).

^1H NMR (300 MHz, CDCl_3) δ ppm 7.12 (t, $J=8.0\text{ Hz}$, 1H), 6.65–6.56 (m, 2H), 6.45–6.41 (m, 1H), 5.33 (br, 1H), 3.71–3.66 (m, 1H), 0.76–0.73 (m, 4H).

Test Examples

Test Example 1

Assay of in vitro DPP-IV inhibitory action

Human serum or bovine plasma containing the DPP-IV enzyme was diluted with assay buffer (25 mM Tris-HCl, 140 mM NaCl, 10 mM KCl, pH 7.9) for use in tests (bovine plasma: final 5-fold dilution; human serum: final 10-fold dilution). Test compound solutions of varying concentration were added prior to incubation at room temperature, followed by the addition of substrate (Glycyl-L-Proline 4-Methyl-Coumaryl-7-Amide, Peptide Laboratories) to a final concentration of 100 μM , and a reaction was brought about at room temperature. Acetic acid was added to a final concentration of 12.5% to stop the reaction, and the fluorescent intensity was determined using a fluorescent plate reader at an excitation wavelength of 360 nm and a measurement wavelength of 460 nm. The compound concentration resulting in 50% inhibition was calculated as the IC_{50} value from the enzyme inhibitory activity at the time the test compounds of varying concentration were added. The mean results of the second through seventh tests are given in Table 1.

(Table 1)

Test Compounds	DPP IV inhibitory activity IC ₅₀ (nM)	
	Bovine	Human
Example 3	8	—
Example 16	14	8
Example 25	16	—
Example 28	1	3
Example 29	5	—
Example 64	13	7
Example 61	27	10
Example 68	56	17
Example 73	40	21
Example 74	89	67
Example 52	17	9
Example 49	14	6
Example 53	21	8
Example 76	12	6
Example 91	27	10
Example 46	80	54
Example 45	23	7
Example 60	41	18
Example 39	24	15
Example 93	10	8
Example 94	65	22
Example 72	30	24
Example 71	193	104
Example 92	22	9
Example 108	7	2
Example 107	7	2

(—: not detected)

Test Example 2Assay of DPP-IV inhibitory activity in rat blood

SD rats were orally dosed with a 0.5% MC suspension of test compounds in doses of 3 mg/kg. 0.5% MC solution alone was given as the control. Blood samples were taken from the caudal vein prior to dosing and 1, 2, 4, 6, and 24 hours after dosing, and the samples were immediately centrifuged to separate the plasma. The resulting plasma was diluted with assay buffer (25 mM Tris-HCl, 140 mM NaCl, 10 mM KCl, pH 7.9) (final 20-fold dilution), substrate (Glycyl-L-Proline 4-Methyl-Coumaryl-7-Amide, Peptide

Laboratories) was added to a final concentration of 100 μ M in the same manner as in Test Example 1, and a reaction was brought about at room temperature. Acetic acid was added to a final concentration of 12.5% to stop the reaction, and the fluorescent intensity was determined using a fluorescent plate reader at an excitation wavelength of 360 nm and a measurement wavelength of 460 nm. The proportion of DPP-IV activity in plasma after administration of the test compounds relative to the DPP-IV activity in plasma before administration was calculated to determine the DPP-IV inhibition in plasma. The area under curve (AUC_{0-24h}) was also calculated in graphs plotting the DPP-IV inhibition as a comprehensive indicator of the *in vivo* DPP-IV inhibiting activity of the test compounds. The results are given in Table 2.

(Table 2)

Test Compounds	Inhibition (%) at each point in time after administration of test compounds					AUC_{0-24h} (% \times h)
	1h	2h	4h	6h	24h	
Example 64	24	21	28	23	1	347
Example 67	80	79	75	71	31	1340
Example 68	69	72	74	63	30	1229
Example 73	64	69	69	61	28	1176
Example 72	57	56	61	49	16	902
Example 71	23	28	29	26	11	476

(n=3)

Test Example 3

Assay of DPP-IV inhibitory activity in mouse blood

C57BL mice on a high fat diet were orally dosed with a 0.5% MC suspension of test compounds in doses of 3 mg/kg. 0.5% MC solution alone was given as the control. Blood samples were taken from the caudal vein prior to dosing and 2, 4, 6, 10, and 24 hours after dosing, and the samples were immediately centrifuged to separate the plasma. The resulting plasma was diluted with assay buffer (25 mM Tris-HCl, 140 mM NaCl, 10 mM KCl, pH 7.9) (final 20-fold dilution), substrate (Glycyl-L-Proline 4-Methyl-Coumaryl-7-Amide, Peptide Laboratories) was added to a final concentration of 100 μ M in the same manner as in Test Example 1, and a reaction was brought about at room temperature. Acetic acid was added to a final concentration of 12.5% to stop the reaction, and the fluorescent intensity was determined using a fluorescent plate reader at an excitation wavelength of 360 nm and a measurement wavelength of 460 nm. The proportion of DPP-IV activity in plasma after administration of the test compounds relative to the DPP-IV activity in plasma before administration was calculated to determine the DPP-IV

inhibition in plasma. The area under curve (AUC(0-24h)) was also calculated in graphs plotting the DPP-IV inhibition as a comprehensive indicator of the *in vivo* DPP-IV inhibiting activity of the test compounds. The results are given in Table 3.

(Table 3)

Test Compounds	Inhibition (%) at each point in time (h) after administration of test compounds				AUC _{0-24h} (% × h)
	2h	4h	6h	24h	
Example 64	17	17	22	47	1597
Example 39	37	60	79	87	533
Example 93	60	73	79	88	451
Example 94	43	69	76	86	543

(n=2 to 4)

Test Example 4

Concentration of test compound in serum during oral administration to rats (compound of Example 49)

After the administration of the compound of Example 49, serum was treated by liquid-liquid extraction. That is, SD rats (males, 7-weeks old) were orally dosed with a 0.5% MC suspension of the compound of Example 49 in doses of 10 mg/kg (5 mL/kg). The concentration of the compound of Example 49 in serum was determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS). That is, 100 μ L internal reference (0.5 μ g/mL) was added to 0.1 mL rat serum and stirred for about 10 seconds by a mixer. To this were added 1 mL standard buffer (pH 6.86, Wako Pure Chemicals) and 3 mL ethyl acetate, and the mixtures were then vertically shaken for 10 minutes and extracted, and were then centrifuged (3,000 rpm, room temperature, 10 min). The organic layer was separated and evaporated to dryness at 40°C under a nitrogen stream, methanol 0.1 mL and water 0.1 mL were added to the resulting residue, the mixture was stirred for about 10 seconds by a mixer, and the 2 μ L of the resulting solution was measured by LC/MS/MS.

For the LC, the column was a Cadenza CD-C18 (50 mm long, 4.6 mm in diameter, 3 μ m particle diameter). The eluant was a 10 mM ammonium acetate aqueous solution/methanol (2:8) mixture, and the flow rate was 0.2 mL/min. A TSQ7000 LC/MS/MS System (ThermoFinnigan) was used for the MS, ESI ionization was employed, positive ions were used in measurement mode, and monitoring was done by SRM (Selective Reaction Monitoring). Table 4 gives the mean concentration in serum at each blood sample time point after oral administration.

Concentration of test compound in serum after oral administration to rats (compound of Example 45 or 76)

After the administration of the compound of Example 45 or 76, serum was treated by solid phase extraction. That is, SD rats (males, 7-weeks old) were orally dosed with a 0.5% MC suspension of the compound of Example 45 or 76 in doses of 10 mg/kg (5 mL/kg). 400 μ L internal reference (0.05 μ g/mL) was added to 0.05 mL rat serum after administration, and the contents were mixed by being inverted. An automated solid phase extractor was employed in the solid phase extraction and concentration of 100 μ L of the solution, which was introduced into the MS/MS apparatus for measurement.

The automated solid phase extractor was a Prospekt-2 (Spark), and the solid phase cartridge was an ODS cartridge. For the LC, the analysis column was a Mightysil RP-18 GP (50 mm long, 2.1 mm in diameter, 3 μ m particle diameter), and the gradient method was employed for elution using a mixture of 10 mM ammonium acetate aqueous solution/methanol. An API4000 LC/MS/MS System (Applied Biosystem) was used for the MS, ESI ionization was employed, positive ions were used in measurement mode, and monitoring was done by MRM (Multiple Reaction Monitoring). Table 4 gives the mean concentration in serum at each blood sample time point after oral administration.

(Table 4) Concentration of test compound in serum after oral administration to rats

Test Compound	Concentration of drug in plasma: units (ng/mL)						
	15 min	30 min	1 hour	2 hours	4 hours	6 hours	24 hours
Example 49	ND	ND	ND	ND	12.7	41.2	ND
Example 45	10.5	30.9	37.4	55.3	149.0	264.0	88.3
Example 76	17.2	69.9	99.9	123.0	208.0	224.0	32.9

ND: under detection limit (10 ng/mL)

Test Example 5

Concentration of test compound in serum after intravenous administration to rats (compound of Example 49)

An aqueous solution (normal saline/0.1 N aqueous hydrochloric acid = 9/1) of the compound of Example 49 was given by intravenous administration in a dose of 1 mg/kg (5 mL/kg) to the caudal vein of SD rats (males, 7-weeks old). The concentration of the compound of Example 49 was then determined in the same manner as for the compound

of Example 49 in Test Example 4. Table 5 gives the mean concentration in serum at each blood sampling time point after intravenous administration.

Concentration of test compound in serum after intravenous administration to rats (compound of Example 49 or 76)

An aqueous solution (50% polyethylene glycol/0.1 N aqueous hydrochloric acid = 9/1) of the compound of Example 45 or an aqueous solution (12% polyethylene glycol) of the compound of Example 76 was given by intravenous administration in a dose of 1 mg/kg (5 mL/kg) to the caudal vein of SD rats (males, 7-weeks old). The concentration of the compound of Example 45 or 76 was then determined in the same manner as for the compound of Example 45 or 76 in Test Example 4. Table 5 gives the mean concentration in serum at each blood sampling time point after intravenous administration.

(Table 5) Concentration of test compound in serum after intravenous administration to rats

Test Compound	Concentration of drug in plasma: units (ng/mL)							
	5 min	15 min	30 min	1 hour	2 hours	4 hours	6 hours	24 hours
Example 49	98.5	66.8	45.7	37.7	24.2	16.7	9.79	ND
Example 45	41.2	27.1	27.0	28.0	36.7	29.9	32.3	9.85
Example 76	59.2	39.9	30.5	36.5	32.3	23.9	29.7	2.96

ND: under detection limit (10 ng/mL)

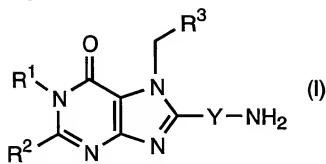
Industrial Applicability

The present invention can provide compounds that have DPP-IV inhibitory activity and that are safer and less toxic, etc.

The compounds of the present invention are useful for controlling prediabetic postprandial hyperglycemia, treating non-insulin-dependent diabetes, treating autoimmune diseases such as arthritis and rheumatoid arthritis, treating intestinal mucosal diseases, stimulating growth, controlling rejection of organ transplants and grafts, treating obesity, treating eating disorders, treating HIV infection, controlling metastasis, treating prostatic hypertrophy, treating pericementitis, and treating osteoporosis.

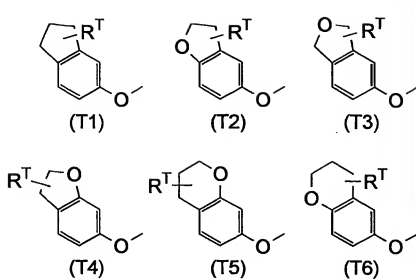
CLAIMS

1. Compounds represented by Formula (I), prodrugs thereof, or pharmaceutically acceptable salts thereof.



[Where R^1 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

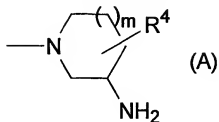
R^2 is a hydrogen atom, a halogen atom, a cyano group, a formyl group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkyloxy group, an optionally substituted alkenyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted alkoxy carbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aryloxy carbonyl group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted arylthio group, an optionally substituted arylsulfinyl group, an optionally substituted arylsulfonyl group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, or a group represented by (T1) through (T6) below:



(where R^T may be absent or present in a number of 1 or more, each independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, a carboxy group, an optionally substituted alkoxy carbonyl group, a saturated heterocyclic group, an oxycarbonyl group, or an optionally substituted carbamoyl group, or two R^T groups together may represent methylene, ethylene, trimethylene, tetramethylene, or butenylene, and may be bonded to 1 or 2 ring-forming carbon atoms to form a new ring);

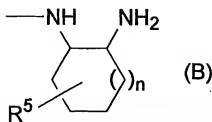
R^3 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted vinyl group, an optionally substituted nitrogen-bearing saturated heterocyclic group, or an optionally substituted heteroaryl group; and

-Y-NH₂ is a group represented by the following Formula (A) or a group represented by the following Formula (B).



(where m is 0, 1 or 2, and R^4 may be absent or present in a number of 1 or 2, each independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group,

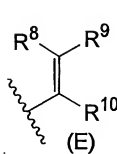
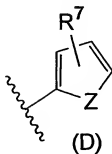
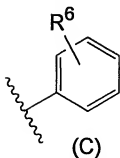
an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxy carbonyl group, or an optionally substituted carbamoyl group, or two R^4 groups together may represent methylene or ethylene, and may be bonded to two ring-forming carbon atoms to form a new ring),



(where n is 0, 1 or 2, and R^5 may be absent or present in a number of 1 or 2, each independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxy carbonyl group, or an optionally substituted carbamoyl group, or two R^5 groups together may represent methylene or ethylene, and may be bonded to two ring-forming carbon atoms to form a new ring).]

2. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 1, wherein $-\text{Y}-\text{NH}_2$ is a group represented by Formula (A), and m is 1 or 2, or $-\text{Y}-\text{NH}_2$ is a group represented by Formula (B), and n is 1 or 2.

3. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 1 or 2, wherein R^3 is any of the groups of Formulas (C), (D), or (E) below.



(where Z is an oxygen atom, -S(O)p-, or -N(R¹¹)-,

R⁶ may be absent or present in a number of 1 or 2, each independently a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, a haloalkoxy group, an optionally substituted amino group, an optionally substituted carbamoyl group, an alkoxycarbonyl group, an optionally substituted alkylcarbonyl group, a cycloalkylcarbonyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group, or two R⁶ groups together may represent a C₁ to C₃ alkylenedioxy group,

R⁷ may be absent or present in a number of 1 or 2, each independently a halogen atom, a cyano group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, or a haloalkoxy group,

R⁸ is methyl, ethyl, a chlorine atom, or a bromine atom,

R⁹ is a hydrogen atom, methyl, ethyl, a chlorine atom, or a bromine atom,

R¹⁰ is a hydrogen atom, methyl, or ethyl,

p is 0, 1 or 2, and

R¹¹ is a hydrogen atom or an alkyl group.)

4. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 3, wherein R³ is Formula (C) or Formula (E).
5. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 4, wherein R³ is Formula (C), and R⁶ may be absent or present in a number of 1 or 2, each independently a halogen atom, a cyano group, an alkylthio group, an alkylsulfonyl group, a C₁ to C₃ alkylenedioxy group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, a haloalkoxy group, an alkoxycarbonyl group, an alkylcarbonyl group, a haloalkylcarbonyl group, or a cycloalkylcarbonyl group.
6. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 4, wherein R³ is Formula (C), and R⁶ is one halogen atom.
7. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 4, wherein R³ is 2-chlorophenyl, 2-chloro-5-fluorophenyl, 2-methyl-5-

fluorophenyl, 2-methoxy-5-fluorophenyl, or 2-cyano-5-fluorophenyl.

8. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 7, wherein R^1 is a hydrogen atom, a C_1 to C_3 optionally substituted alkyl group, or an optionally substituted aryl group, and the substituents for the optionally substituted alkyl groups are selected from a fluorine atom, optionally substituted aroyl groups, a carboxyl group, optionally substituted alkoxy carbonyl groups, optionally substituted aryl groups, and optionally substituted aryloxy groups.

9. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 7, wherein R^1 is a group represented by the formula $-Ra-Rb-Rc$. Where,

Ra is an alkylene chain,

Rb is a single bond or a carbonyl group, and

Rc is an optionally substituted alkyl group, an optionally substituted alkoxy group, an optionally substituted aryl group, or an optionally substituted aryloxy group.

10. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 7, wherein R^1 is a hydrogen atom, methyl, or ethyl.

11. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 7, wherein R^1 is methyl.

12. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 11, wherein R^2 is a hydrogen atom, a cyano group, an optionally substituted alkyl, a carboxy group, an optionally substituted alkoxy group, an optionally substituted alkoxy carbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, and optionally substituted aryloxy carbonyl group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, or an optionally substituted alkyl carbonyl group.

13. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 11, wherein R^2 is a cyano group, an optionally substituted alkoxy carbonyl group, or an optionally substituted aryloxy group.

14. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according

to Claim 13, wherein R^2 is a substituted aryloxy group.

15. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 11, wherein R^2 is a substituted heteroaryloxy group.

16. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 11, wherein R^2 is a group represented by (T1) through (T6).

17. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 11, wherein R^2 is a group represented by the formula $-O-Tx-O-Ty$ (where O is an oxygen atom, Tx is a phenylene group, a pyridinediyl group, a pyrimidinediyl group, or a thiophenediyl group, and Ty is an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, or an optionally substituted saturated heterocyclic group).

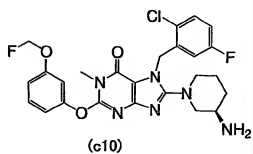
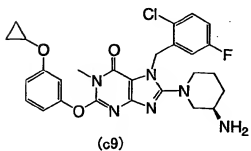
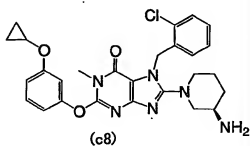
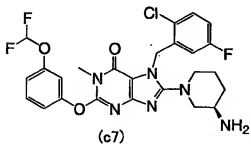
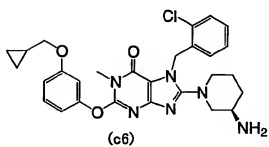
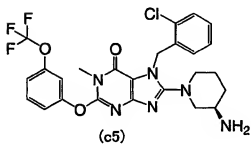
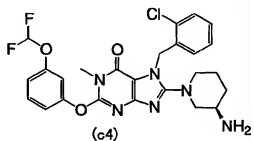
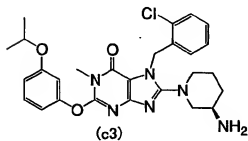
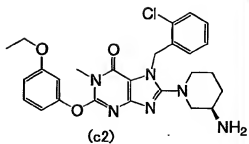
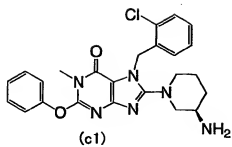
18. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 17, wherein Tx is a phenylene group.

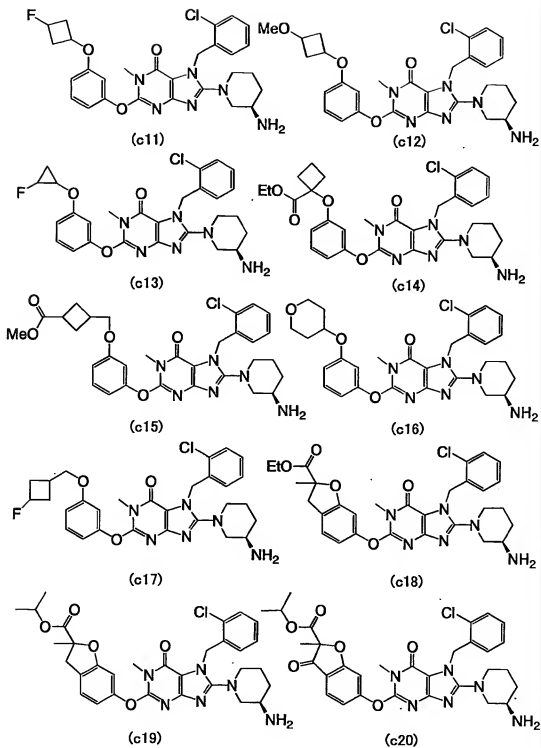
19. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 18, wherein Tx is m-phenylene.

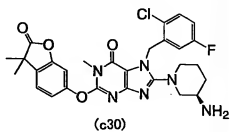
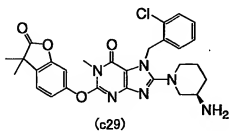
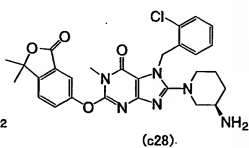
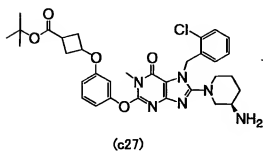
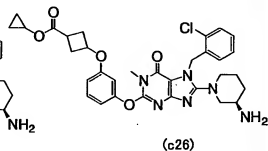
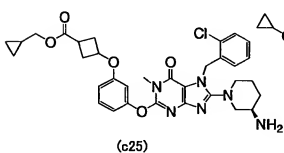
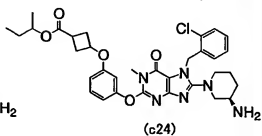
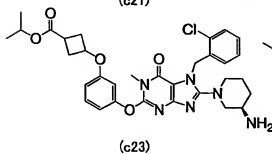
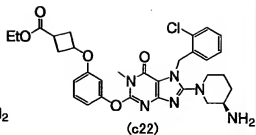
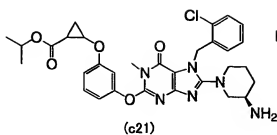
20. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 19, wherein Ty is a substituted alkyl group, a substituted cycloalkyl group, or an optionally substituted cycloalkylalkyl group.

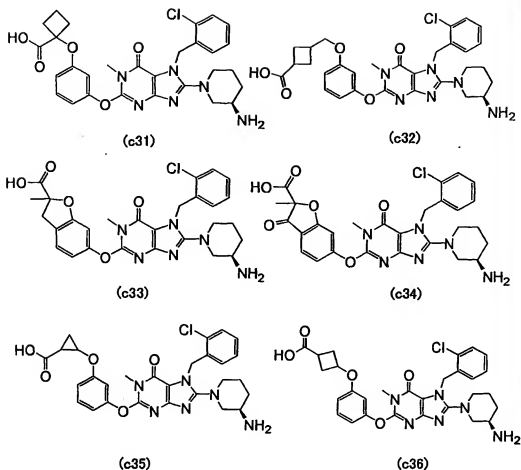
21. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 20, wherein the substituents for groups represented by Ty are halogen atoms, carboxy groups, or alkoxy carbonyl groups.

22. Compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to Claim 1, wherein compounds represented by Formula (I) the following Formulas (ccl) through (c36):









23. Pharmaceuticals comprising as an active ingredient a compound, prodrug thereof, or pharmaceutically acceptable salt thereof according to any of Claims 1 through 22.

24. Dipeptidyl peptidase-IV inhibitors comprising as an active ingredient a compound, prodrug thereof, or pharmaceutically acceptable salt thereof according to any of Claims 1 through 22.

25. Therapeutic agents for diabetes comprising as an active ingredient a compound, prodrug thereof, or pharmaceutically acceptable salt thereof according to any of Claims 1 through 22.

26. Uses of compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 22 to produce dipeptidyl peptidase-IV inhibitors.

27. Uses of compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof

according to any of Claims 1 through 22 to produce therapeutic agents for diabetes.

28. Methods for treating diabetes, comprising the administration of effective amounts of compounds, prodrugs thereof, or pharmaceutically acceptable salts thereof according to any of Claims 1 through 22 to patients requiring treatment.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/006104

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.⁷ C07D, 473/30, 473/18, 473/06, 473/04, 473/22, A61K31/52,
31/5377, A61P43/00, 29/00, 19/02, 37/06, 1/00, 3/04, 31/18,
35/04, 13/08, 19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.⁷ C07D, 473/30, 473/18, 473/06, 473/04, 473/22, A61K31/52,
31/5377, A61P43/00, 29/00, 19/02, 37/06, 1/00, 3/04, 31/18,
35/04, 13/08, 19/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY (STN), CAPLUS (STN), CAOLD (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 04/018469 A1 (BOEHRINGER INGELHEIM PHARMA G.M.B.H. & CO. K.G.), 04 March, 2004 (04.03.04), Full text & DE 10238477 A1 & US 2004/122228 A1	1-27
P, X	WO 03/104229 A1 (Eisai Co., Ltd.), 18 December, 2003 (18.12.03), Full text & US 2004/116328 A1	1-27
A	WO 03/024965 A2 (NOVO NORDISK A/S), 27 March, 2003 (27.03.03), & US 2003/199528 A1	1-27

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

Date of the actual completion of the international search
30 June, 2004 (30.06.04)

Date of mailing of the international search report
20 July, 2004 (20.07.04)

Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

ECT/JP2004/006104

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/004496 A1 (NOVO NORDISK A/S), 16 January, 2003 (16.01.03), & EP 1404675 A1 & US 2003/105077 A1	1-27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/006104

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 28 pertains to methods for treatment of the human body by therapy.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. C17 C07D, 473/30, 473/18, 473/06, 473/04, 473/22,
A61K31/52, 31/5377, A61P43/00, 29/00, 19/02, 37/06, 1/00,
3/04, 31/18, 35/04, 13/08, 19/10

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. C17 C07D, 473/30, 473/18, 473/06, 473/04, 473/22,
A61K31/52, 31/5377, A61P43/00, 29/00, 19/02, 37/06, 1/00,
3/04, 31/18, 35/04, 13/08, 19/10

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で利用した電子データベース (データベースの名称、調査に使用した用語)

REGISTRY (STN), CAPLUS (STN), CAOLD (STN)

C. 関連すると認められる文献

引用文献の カテゴリ	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
P X	WO 04/018469 A1 (BOEHRINGER INGELHEIM PHARMA G.M.B.H & CO. K. G.) 2004.03.04 全文参照 & DE 10238477 A1 & US 2004/122228 A1	1-27
P X	WO 03/104229 A1 (エーザイ株式会社) 2003.12.18 全文参照 & US 2004/116328 A1	1-27

☒ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリ

「A」特に関連のある文献ではなく、一般の技術水準を示すもの

「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの

「L」優先権主張に取拠を要する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)

「O」口頭による開示、使用、展示等に言及する文献

「P」国際出願日前で、かつ優先権の主張の基礎となる出願

の日後に公表された文献

「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「Z」同一パテントファミリー文献

国際調査を完了した日

30.06.2004

国際調査報告の発送日

20.7.2004

国際調査機関の名称及びあて先

日本国特許庁 (ISA/JP)

郵便番号100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

中本 亜希

4P 9282

電話番号 03-3581-1101 内線 3492

様式PCT/ISA/210 (第2ページ) (2004年1月)

C (続き) 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
A	WO 03/024965 A2 (NOVO NORDISK A/S) 2003.03.27 & US 2003/199528 A1	1-27
A	WO 03/004496 A1 (NOVO NORDISK A/S) 2003.01.16 & EP 1404675 A1 & US 2003/105077 A1	1-27

第II欄 請求の範囲の一部の調査ができないときの意見 (第1ページの2の続き)

法第8条第3項 (PCT17条(2)(a))の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1. ☒ 請求の範囲 28 は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、
請求の範囲 28 は、治療による人体の処置方法に関するものである。
2. ☐ 請求の範囲 _____ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、
3. ☐ 請求の範囲 _____ は、従属請求の範囲であってPCT規則6.4(a)の第2文及び第3文の規定に従って記載されていない。

第III欄 発明の単一性が欠如しているときの意見 (第1ページの3の続き)

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1. ☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。
2. ☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。
3. ☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったため、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。
4. ☐ 出願人が必要な追加調査手数料を期間内に納付しなかったため、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

- ☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。